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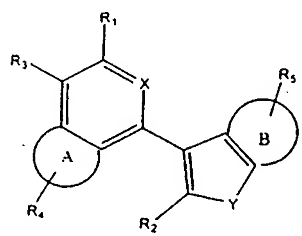

(1)

(57) Abstract

The present invention relates to heterocyclic antibacterial agents with antimicrobial activity, and particularly, antibacterial activity against both sensitive and resistant strains, represented by general formula (1), or a pharmaceutically acceptable salt and/or prodrug thereof, wherein each of A and B independently represent fused rings selected from a group consisting of monocyclic or polycyclic cycloalkyls, cycloalkenyls, aryls, and heterocyclic rings, said rings comprising from 4 to 8 atoms in a ring structure: X represents CR, N, N(O), P, or As; Y represents CR_2, NR, O, PR, S, AsR, or Se.

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ISOQUINOLINE–INDOLE COMPOUNDS AS ANTIMICROBIAL AGENTS

Background of the Invention

A number of structural classes of compounds with antibacterial properties are known. Historically, the most important classes of antibacterials have been the β-lactams, macrolides, lincosamides, aminoglycosides, tetracyclines, polypeptides, and sulfonamides. The bulk of these antibacterial compounds were isolated originally from molds, fungi or bacteria; synthetic and semi-synthetic compounds, additionally, have proven to be efficacious in the treatment of bacterial infections. In the broadest possible sense, known antibacterials work by influencing at least one of the following cellular processes or characteristics: cell wall synthesis; protein synthesis; nucleic acid synthesis; cellular metabolism; and cytoplasmic membrane permeability. Brief descriptions follow of the mechanisms of action of members of each of the aforementioned classes of antibacterials.

The β-lactam antibiotics inhibit penicillin binding proteins (PBPs). The PBPs are ubiquitous bacterial enzymes that are involved in cell wall biosynthesis (reviewed in Waxman et al., 1983 Annual Review of Biochemistry 58:825-869; Georgopapadkou et al., 1983 Handbook of Experimental Pharmacology 67:1-77; and Ghuysen, 1991 Annual Review of Microbiology 45:37-67); inhibition of these proteins disrupts the biosynthesis of the bacterial cell wall. Specifically, these compounds act as substrate analogs for the PBPs and form an acyl enzyme intermediate. This acyl enzyme intermediate is resistant to subsequent hydrolysis and ties up the enzyme in a relatively long-lived inactive form. Bacteria have responded to the widespread use of β-lactam antibiotics by evolving a class of β-lactam hydrolyzing enzymes known as β-lactamases. These enzymes are one of the sources of drug resistance now being observed in a number of bacterial diseases including tuberculosis, malaria, pneumonia, meningitis, dysentery, bacteremia, and various venereal diseases.

The macrolides are a family of antibiotics whose structures contain large lactone rings linked through glycoside bonds with amino sugars. The most important members of the group are erythromycin and oleandomycin. Erythromycin is active against most Gram-positive bacteria, *Neisseria*, *Legionella* and *Haemophilus*, but not against the *Enterobacteriaceae*. Macrolides inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit. Binding inhibits elongation of the protein by peptidyl transferase or prevents translocation of the ribosome or both. Macrolides are bacteriostatic for most bacteria but are bactericidal for a few Gram-positive bacteria.

The lincosamides are sulfur-containing antibiotics isolated from *Streptomyces lincolnensis*. There are two important lincosamides: lincomycin and clindamycin. Clindamycin is preferred over lincomycin due to its greater potency, fewer adverse side effects, and its more

favorable pharmacokinetic properties. Bacterial resistance and cross resistance to clindamycin have begun to emerge. The lincosamides are active against Gram-positive bacteria especially *cocci*, but also non-spore forming anaerobic bacteria, *Actinomycetes*, *Mycoplasm* and some *Plasmodium*. The lincosamides bind to the 50S ribosomal subunit and thereby inhibit protein synthesis. These drugs may be bacteriostatic or bactericidal depending upon several factors, including their local concentration.

Aminoglycosides are important antibacterials used primarily to treat infections caused by susceptible aerobic Gram-negative bacteria. Unfortunately, they have a narrow margin of safety, producing characteristic lesions in kidney, cochlea, and vestibular apparatus within the therapeutic dose range. Because they are polycations, the aminoglycosides cross cellular membranes very poorly.

The tetracyclines consist of eight related antibiotics which are all natural products of *Streptomyces*, although some can now be produced semi-synthetically. Tetracycline, chlortetracycline and doxycycline are the best known members of this class. The tetracyclines are broad-spectrum antibiotics with a wide range of activity against both Gram-positive and Gram-negative bacteria. The tetracyclines act by blocking the binding of aminoacyl tRNA to the A site on the ribosome. Tetracyclines inhibit protein synthesis on isolated 70S or 80S (eukaryotic) ribosomes, and in both cases, their effect is on the small ribosomal subunit. Most bacteria possess an active transport system for tetracycline that will allow intracellular accumulation of the antibiotic at concentrations 50 times as great as that in the surrounding medium. This system greatly enhances the antibacterial effectiveness of tetracycline and accounts for its specificity of action, since an effective concentration is not accumulated in host cells. Thus a blood level of tetracycline which is harmless to mammalian tissues can halt protein synthesis in invading bacteria. The tetracyclines have a remarkably low toxicity and minimal side effects in mammals. The combination of their broad spectrum and low toxicity has led to their overuse and misuse by the medical community and the wide-spread development of resistance has reduced their effectiveness. Nonetheless, tetracyclines still have some important uses, such as in the treatment of Lyme disease.

The polypeptide antibacterials have in common their basic structural elements -- amino acids. Representatives of this class include vancomycin, and bacitracin. Vancomycin can be used to treat both systemic and gastrointestinal infections, whereas because of serious systemic toxicities bacitracin, is limited to topical applications. Vancomycin inhibits bacterial cell wall synthesis by inhibiting peptidoglycan synthase, apparently by binding to D-alanyl-D-alanine, a component of the cross-link between chains. This action inhibits peptidoglycan chain elongation, and as might be expected, the effect is bactericidal for most organisms if they are dividing rapidly. Because it does not target penicillin-binding enzymes, vancomycin is not cross-resistant with the β-lactams. Bacitracin is a narrow spectrum antibiotic which inhibits cell

wall biosynthesis by inhibiting lipid pyrophosphatase; this enzyme is involved in transmembrane transport of peptidoglycan precursors.

The sulphonamides are usually bacteriostatic and arrest cell growth by inhibiting bacterial folic acid synthesis. They are effective against sensitive strains of Gram-negative and Gram-positive bacteria, *Actinomyces*, *Nocardia* and *Plasmodia*. However, extensive clinical use of sulfonamides over many years has resulted in a high level of resistance and their current use is limited.

Antibacterial resistance is a global clinical and public health problem that has emerged with alarming rapidity in recent years and undoubtedly will increase in the near future. Resistance is a problem in the community as well as in health care settings, where transmission of bacteria is greatly amplified. Because multiple drug resistance is a growing problem, physicians are now confronted with infections for which there is no effective therapy. The morbidity, mortality, and financial costs of such infections pose an increasing burden for health care systems worldwide, but especially in countries with limited resources. Strategies to address these issues emphasize enhanced surveillance of drug resistance, increased monitoring and improved usage of antimicrobial drugs, professional and public education, development of new drugs, and assessment of alternative therapeutic modalities.

Summary of the Invention

There exists a need to provide alternative and improved agents for the treatment of bacterial infections particularly for the treatment of infections caused by resistant strains of bacteria, e.g. penicillin-resistant, methicillin-resistant, ciprofloxacin-resistant, and/or vancomycin-resistant strains, as well as for the decontamination of objects bearing such organisms, e.g. non-living matter, hospital equipment, walls of operating rooms, and the like.

In general, the present invention provides a method and pharmaceutical preparations for inhibiting the growth of bacterial microorganisms, such as in the treatment of Gram-positive infections, including *Staphylococcus* infections, *Streptococcus* infections, and *Enterococcus* infections, and in the treatment of Gram-negative infections, including *Enterobacteriaceae* infections, *Mycobacterium* infections, *Neisseria* infections, *Pseudomonas* infections, *Shigella* infections, *Escherichia* infections, *Bacillus* infections, *Micrococcus* infections, *Arthrobacter* infections, and *Peptostreptococcus* infections. For instance, the compounds of the present invention are particularly useful in the treatment of infections caused by methicillin-resistant strains of bacteria, e.g., methicillin-resistant strains of *Staphylococcus aureus* (MRSA; *Micrococcus pyogenes var. aureus*), and ciprofloxacin-resistant strains of bacteria, e.g., ciprofloxacin-resistant strains of *Staphylococcus aureus* (CRSA). In preferred embodiments, the present invention can be used to inhibit bacterial infections caused by Gram-positive bacteria, for example, *S. aureus*, *S. epidermidis*, *S. pneumonia*.

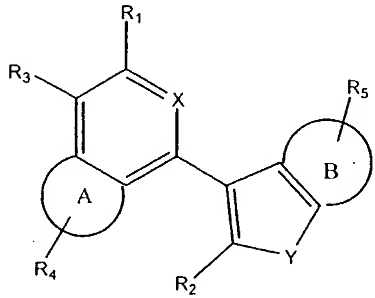
The invention, as described herein, is directed to the use of novel small (e.g., M_r < 1.5 kD) organic molecules, e.g., 1-(3-indolyl)-isoquinolines and substituted derivatives thereof, and pharmaceutical formulations thereof, in the treatment of bacterial infections. Specifically proposed as antibacterial agents are compounds based on 1-(3-indolyl)-3-isoquinolinecarboxamide, and derivatives thereof, and 1-(3-indolyl)isoquinoline, and derivatives thereof. Many of the antibacterials contemplated herein are expected, based on data for numerous corresponding 2-(3-indolyl)-4-quinolinecarboxamides and 2-(3-indolyl)quinolines, to have *in vitro* minimum inhibitory concentrations (MICs) at or below single-digit micromolar concentrations in assays against cultures of methicillin-resistant *Staphylococcus aureus* (MRSA), ciprofloxacin-resistant *Staphylococcus aureus* (CRSA), vancomycin-resistant *Enterococcus* spp. (VRE), and/or penicillin-resistant *Pseudomonas* (PRP).

Detailed Description of the Invention

In the last decade, the frequency and spectrum of antimicrobial-resistant infections has increased. Certain infections that are essentially untreatable are reaching epidemic proportions in both the developing world and institutional settings in the developed world. Antimicrobial resistance is manifested in increased morbidity, mortality, and health-care costs. *Staphylococcus aureus* is an significant cause of nosocomial infection, especially nosocomial pneumonia, surgical wound infection, and bloodstream infection (Panlilio et al., Infect. Cont. Hosp. Epidemiol. 13: 582-586 (1992)). Other pathogens commonly associated with nosocomial infection include, but are not limited to, *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus* spp., *Enterobacter* spp., coagulase-negative *staphylococci* (CNS). As described above, a considerable amount of effort has been devoted to developing bacteriostatic and bactericidal agents with activity against these and other microorganisms.

The present invention relates to heterocyclic antibacterial agents with antimicrobial activity, and particularly, antibacterial activity against both sensitive and resistant strains. The subject antibacterial compounds comprise two distinct heterocycles that are covalently linked to each other, preferably via a carbon-carbon single bond. In preferred embodiments, the individual heterocyclic moieties are isoquinoline and indole nuclei interconnected at their respective 1- and 3-positions. Three preferred subclasses of the compounds are disclosed: 1) a subclass in which the substituent at the 3-position of the isoquinoline nucleus comprises a primary or secondary amine; 2) a subclass in which the substituent at the 3-position of the isoquinoline nucleus is a hydrogen, halogen, or another group that does not comprise a primary or secondary amine; and 3) a subclass in which a substituent on the B-ring of the isoquinoline nucleus is a 1-alkynyl group. The remaining positions of the 1-isoquinolinyl and 3-indolyl nuclei of the subject compounds may independently be unsubstituted or substituted with a variety of groups giving rise to a variety of antimicrobial compounds.

For example, in one embodiment, the compounds of the present invention are represented by the general formula 1, or a pharmaceutically acceptable salt and/or prodrug thereof:



1

wherein

each of A and B independently represent fused rings selected from a group consisting of monocyclic or polycyclic cycloalkyls, cycloalkenyls, aryls, and heterocyclic rings, said rings comprising from 4 to 8 atoms in a ring structure;

X represents CR, N, N(O), P, or As;

Y represents CR_2, NR, O, PR, S, AsR, or Se;

R, R_1, R_2, and R_3, for each occurrence, independently represent hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

R_4 and R_5, for each occurrence, independently represent halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

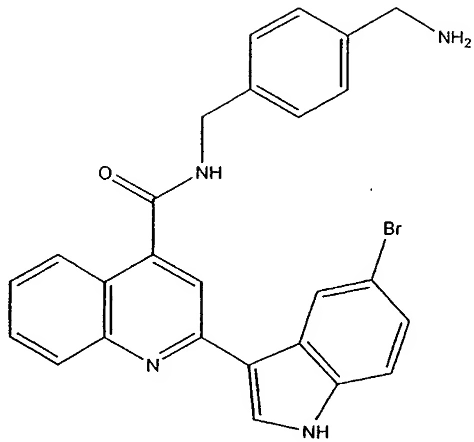
A and B independently may be unsubstituted or substituted with R_4 and R_5, respectively, any number of times up to the limitations imposed by stability and the rules of valence;

R_1 and R_3 taken together may represent a ring comprising a total of 3-7 atoms in the backbone of said ring; said ring may comprise one or two heteroatoms in its backbone; and said ring may bear additional substituents or be unsubstituted;

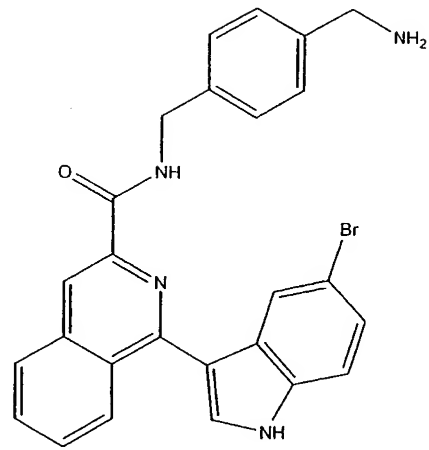
R_{80} represents an unsubstituted or substituted aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

The subject compounds should be effective against a number of human and veterinary pathogens, including Gram-positive bacteria such as multiply-resistant staphylococci, streptococci and enterococci, and are expected to be active against Gram-negative organisms as well, such as *Bacteroides spp.* and *Clostridia spp.* species, and acid-fast organisms such as *Mycobacterium tuberculosis*, *Mycobacterium avium* and other *Mycobacterium spp.*, and in organisms such as *Mycoplasma spp.* The MIC data in Examples 10 and 11 establish the activity of the compounds against these pathogens: Example 8 recites MIC values for four-hundred-and-eighty-two 2-(3-indolyl)quinolines against MRSA, VREF, and/or *S. pneumonia*; and Example 7 recites MIC values for a 1-(3-indolyl)isoquinoline against MRSA and VREF. A comparison, of the data in Example 8 for 9 to the data in Example 7 for the analogous 1-(3-indolyl)isoquinoline, indicates that the 1-(3-indolyl)isoquinoline antibacterials will have activity comparable to that of the corresponding 2-(3-indolyl)quinoline antibacterials. It is contemplated that the compounds of the invention can be used in combating and/or eliminating an infectious process caused by a microorganism in a host. In a particular aspect of the invention, the high potency and rapid bactericidal activity of these compounds make them attractive candidates for use in preventative therapies, such as sterilization of wounds prior to suture, as well as the sterilization of instruments prior to their use in surgical or other invasive procedures.



Example 8, 9



Example 7

Compound	Bacterium	MIC (μg/mL)
Example 8, 9	MRSA	< 7
Example 7	MRSA	< 7
Example 8, 9	VREF	< 7
Example 7	VREF	< 25
Example 8, 9	*S. pneumonia*	< 7

The invention is also directed to methods for treating a microbial infection in a host using the compositions of the invention. For instance, the subject method can be used to treat or prevent nosocomial bacteremia and skin/wound infection, or lower respiratory infection, endocarditis, and infections of the urinary tract. According to the present invention, treatment of such bacterial diseases comprises the administration of a pharmaceutical composition of the invention in a therapeutically effective amount to an individual in need of such treatment. The compositions may be administered parenterally by intramuscular, intravenous, intraocular, intraperitoneal, or subcutaneous routes; inhalation; orally, topically and intranasally.

Their antimicrobial activity also renders the compounds of the invention particularly useful in inhibiting unwanted microbial growth in tissue culture, especially those used for production of recombinant proteins or vectors for use in gene therapy.

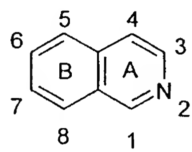
The invention is also directed to pharmaceutical compositions, comprising one or more of the antimicrobial compounds of the invention as the active ingredient(s), which may be administered to a host animal.

I. Definitions

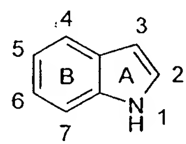
For convenience, certain terms employed in the specification, examples, and appended claims are collected here.

As used herein, the term "antimicrobial" refers to the ability of the compounds of the invention to prevent, inhibit or destroy the growth of microbes such as bacteria, fungi, protozoa and viruses.

The terms "isoquinoline" and "indole" are intended to mean compounds having the following general chemical structures, wherein the numbers around their peripheries indicate the art-recognized positional designations for the two ring systems, and the capital letters contained within the individual rings are, likewise, their art-recognized descriptors:

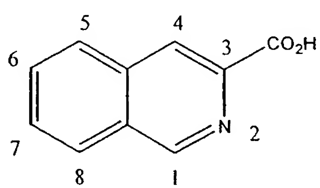


isoquinoline

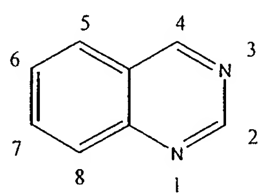


indole

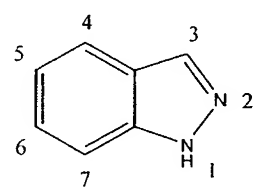
An analog of an isoquinoline or indole is intended to mean any derivative, which adheres to the rules of valence, of an isoquinoline or indole, in particular derivatives in which a nitrogen is replaced by another atom, derivatives in which any of the carbon atoms are replaced with another heavy atom, and derivatives in which additional chemical groups are attached to any of the heavy atoms of the molecule. For example, the present invention contemplates the use of derivatives of 3-isoquinolinecarboxylic acid, quinazoline and 1*H*-indazole:



3-isoquinolinecarboxylic acid



quinazoline



*1*H*-indazole*

The term "prodrug" is intended to encompass compounds which, under physiological conditions, are converted into the antibacterial agents of the present invention. A common method for making a prodrug is to select moieties, e.g., for any of the R_1-R_5 substituents of

formula 1, which are hydrolyzed under physiological conditions to provide the desired compound. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal or the target bacteria.

The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are boron, nitrogen, oxygen, phosphorus, sulfur and selenium.

The term "electron-withdrawing group" is recognized in the art, and denotes the tendency of a substituent to attract valence electrons from neighboring atoms, i.e., the substituent is electronegative with respect to neighboring atoms. A quantification of the level of electron-withdrawing capability is given by the Hammett sigma (σ) constant. This well known constant is described in many references, for instance, J. March, <u>Advanced Organic Chemistry</u>, McGraw Hill Book Company, New York, (1977 edition) pp. 251-259. The Hammett constant values are generally negative for electron donating groups ($\sigma[P] = - 0.66$ for NH_2) and positive for electron withdrawing groups ($\sigma[P] = 0.78$ for a nitro group), $\sigma[P]$ indicating para substitution. Exemplary electron-withdrawing groups include nitro, acyl, formyl, sulfonyl, trifluoromethyl, cyano, chloride, and the like. Exemplary electron-donating groups include amino, methoxy, and the like.

Herein, the term "aliphatic group" refers to a straight-chain, branched-chain, or cyclic aliphatic hydrocarbon group and includes saturated and unsaturated aliphatic groups, such as an alkyl group, an alkenyl group, and an alkynyl group.

The term "alkyl" refers to the radical of saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In preferred embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C_1-C_{30} for straight chain, C_3-C_{30} for branched chain), and more preferably 20 or fewer. Likewise, preferred cycloalkyls have from 3-10 carbon atoms in their ring structure, and more preferably have 5, 6 or 7 carbons in the ring structure.

Moreover, the term "alkyl" (or "lower alkyl") as used throughout the specification, examples, and claims is intended to include both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include

substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), $-CF_3$, -CN and the like. Exemplary substituted alkyls are described below. Cycloalkyls can be further substituted with alkyls, alkenyls, alkoxys, alkylthios, aminoalkyls, carbonyl-substituted alkyls, $-CF_3$, -CN, and the like.

The term "aralkyl", as used herein, refers to an alkyl group substituted with an aryl group (e.g., an aromatic or heteroaromatic group).

The terms "alkenyl" and "alkynyl" refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group, as defined above, but having from one to ten carbons, more preferably from one to six carbon atoms in its backbone structure. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths. Throughout the application, preferred alkyl groups are lower alkyls. In preferred embodiments, a substituent designated herein as alkyl is a lower alkyl.

The term "aryl" as used herein includes 5-, 6- and 7-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles" or "heteroaromatics." The aromatic ring can be substituted at one or more ring positions with such substituents as described above, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, $-CF_3$, -CN, or the like. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls.

The abbreviations Me, Et, Ph, Tf, Nf, Ts, Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, nonafluorobutanesulfonyl, *p*-toluenesulfonyl and methanesulfonyl, respectively. A more comprehensive list of the abbreviations utilized by organic chemists of ordinary skill in the art appears in the first issue of each volume of the *Journal of Organic Chemistry*; this list is typically presented in a table entitled Standard List of Abbreviations. The abbreviations contained in said list, and all abbreviations utilized by organic chemists of ordinary skill in the art are hereby incorporated by reference.

The terms *ortho*, *meta* and *para* apply to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and *ortho*-dimethylbenzene are synonymous.

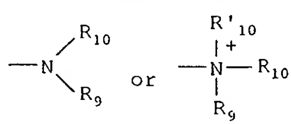
The terms "heterocyclyl" or "heterocyclic group" refer to 3- to 10-membered ring structures, more preferably 3- to 7-membered rings, whose ring structures include one to four heteroatoms. Heterocycles can also be polycycles. Heterocyclyl groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic ring can be substituted at one or more positions with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, or the like.

The terms "polycyclyl" or "polycyclic group" refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, or the like.

The term "carbocycle", as used herein, refers to an aromatic or non-aromatic ring in which each atom of the ring is carbon.

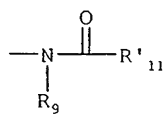
As used herein, the term "nitro" means $-NO_2$; the term "halogen" designates -F, -Cl, -Br or -I; the term "sulfhydryl" means -SH; the term "hydroxyl" means -OH; and the term "sulfonyl" means $-SO_2-$.

The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines, e.g., a moiety that can be represented by the general formula:



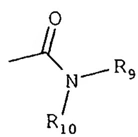
wherein R_9, R_{10} and R'_{10} each independently represent a hydrogen, an alkyl, an alkenyl, $-(CH_2)_m$-R80, or R_9 and R_{10} taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; R80 represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle or a polycycle; and m is zero or an integer in the range of 1 to 8. In preferred embodiments, only one of R_9 or R_{10} can be a carbonyl, e.g., R_9, R_{10} and the nitrogen together do not form an imide. In even more preferred embodiments, R_9 and R_{10} (and optionally R'_{10}) each independently represent a hydrogen, an alkyl, an alkenyl, or $-(CH_2)_m$-R80. Thus, the term "alkylamine" as used herein means an amine group, as defined above, having a substituted or unsubstituted alkyl attached thereto, i.e., at least one of R_9 and R_{10} is an alkyl group.

The term "acylamino" is art-recognized and refers to a moiety that can be represented by the general formula:



wherein R_9 is as defined above, and R'_{11} represents a hydrogen, an alkyl, an alkenyl or $-(CH_2)_m$-R80, where m and R80 are as defined above.

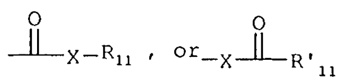
The term "amido" is art recognized as an amino-substituted carbonyl and includes a moiety that can be represented by the general formula:



wherein R_9, R_{10} are as defined above. Preferred embodiments of the amide will not include imides which may be unstable.

The term "alkylthio" refers to an alkyl group, as defined above, having a sulfur radical attached thereto. In preferred embodiments, the "alkylthio" moiety is represented by one of -S-alkyl, -S-alkenyl, -S-alkynyl, and $-S-(CH_2)_m$-R80, wherein m and R80 are defined above. Representative alkylthio groups include methylthio, ethyl thio, and the like.

The term "carbonyl" is art recognized and includes such moieties as can be represented by the general formula:

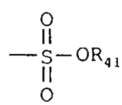


wherein X is a bond or represents an oxygen or a sulfur, and R_{11} represents a hydrogen, an alkyl, an alkenyl, $-(CH_2)_m$-R80 or a pharmaceutically acceptable salt, R'_{11} represents a

hydrogen, an alkyl, an alkenyl or $-(CH_2)_m-R_{80}$, where m and R_{80} are as defined above. Where X is an oxygen and R_{11} or R'_{11} is not hydrogen, the formula represents an "ester". Where X is an oxygen, and R_{11} is as defined above, the moiety is referred to herein as a carboxyl group, and particularly when R_{11} is a hydrogen, the formula represents a "carboxylic acid". Where X is an oxygen, and R'_{11} is hydrogen, the formula represents a "formate". In general, where the oxygen atom of the above formula is replaced by sulfur, the formula represents a "thiolcarbonyl" group. Where X is a sulfur and R_{11} or R'_{11} is not hydrogen, the formula represents a "thiolester." Where X is a sulfur and R_{11} is hydrogen, the formula represents a "thiolcarboxylic acid." Where X is a sulfur and R_{11}' is hydrogen, the formula represents a "thiolformate." On the other hand, where X is a bond, and R_{11} is not hydrogen, the above formula represents a "ketone" group. Where X is a bond, and R_{11} is hydrogen, the above formula represents an "aldehyde" group.

The terms "alkoxyl" or "alkoxy" as used herein refers to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. An "ether" is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxyl, such as can be represented by one of -O-alkyl, -O-alkenyl, -O-alkynyl, $-O-(CH_2)_m-R_{80}$, where m and R_{80} are described above.

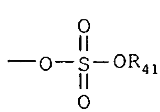
The term "sulfonate" is art recognized and includes a moiety that can be represented by the general formula:



in which R_{41} is an electron pair, hydrogen, alkyl, cycloalkyl, or aryl.

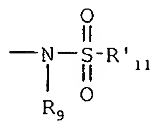
The terms triflyl, tosyl, mesyl, and nonaflyl are art-recognized and refer to trifluoromethanesulfonyl, *p*-toluenesulfonyl, methanesulfonyl, and nonafluorobutanesulfonyl groups, respectively. The terms triflate, tosylate, mesylate, and nonaflate are art-recognized and refer to trifluoromethanesulfonate ester, *p*-toluenesulfonate ester, methanesulfonate ester, and nonafluorobutanesulfonate ester functional groups and molecules that contain said groups, respectively.

The term "sulfate" is art recognized and includes a moiety that can be represented by the general formula:



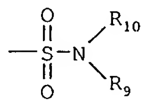
in which R_{41} is as defined above.

The term "sulfonamido" is art recognized and includes a moiety that can be represented by the general formula:



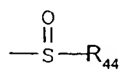
in which R_9 and R'_{11} are as defined above.

The term "sulfamoyl" is art-recognized and includes a moiety that can be represented by the general formula:



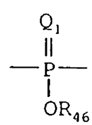
in which R_9 and R_{10} are as defined above.

The terms "sulfoxido" or "sulfinyl", as used herein, refers to a moiety that can be represented by the general formula:

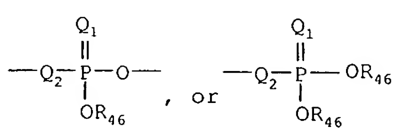


in which R_{44} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aralkyl, or aryl.

A "phosphoryl" can in general be represented by the formula:

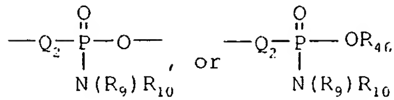


wherein Q_1 represented S or O, and R_{46} represents hydrogen, a lower alkyl or an aryl. When used to substitute, e.g., an alkyl, the phosphoryl group of the phosphorylalkyl can be represented by the general formula:



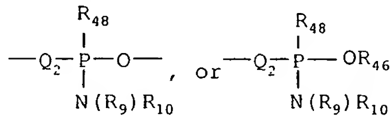
wherein Q_1 represented S or O, and each R_{46} independently represents hydrogen, a lower alkyl or an aryl, Q_2 represents O, S or N. When Q_1 is an S, the phosphoryl moiety is a "phosphorothioate".

A "phosphoramidite" can be represented in the general formula:



wherein R_9 and R_{10} are as defined above, and Q_2 represents O, S or N.

A "phosphonamidite" can be represented in the general formula:



wherein R_9 and R_{10} are as defined above, Q_2 represents O, S or N, and R_{48} represents a lower alkyl or an aryl, Q_2 represents O, S or N.

A "selenoalkyl" refers to an alkyl group having a substituted seleno group attached thereto. Exemplary "selenoethers" which may be substituted on the alkyl are selected from one of -Se-alkyl, -Se-alkenyl, -Se-alkynyl, and $\text{-Se-(CH}_2)_m\text{-R}_{80}$, m and R_{80} being defined above.

Analogous substitutions can be made to alkenyl and alkynyl groups to produce, for example, aminoalkenyls, aminoalkynyls, amidoalkenyls, amidoalkynyls, iminoalkenyls, iminoalkynyls, thioalkenyls, thioalkynyls, carbonyl-substituted alkenyls or alkynyls.

As used herein, the definition of each expression, e.g. alkyl, m, n, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including cis- and trans-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

Contemplated equivalents of the compounds described above include compounds which otherwise correspond thereto, and which have the same general properties thereof (e.g. the

ability to inhibit bacterial cell growth), wherein one or more simple variations of substituents are made which do not adversely affect the efficacy of the compound in inhibiting bacterial cell growth. In general, the compounds of the present invention may be prepared by the methods illustrated in the general reaction schemes as, for example, described below, or by modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are in themselves known, but are not mentioned here.

It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein above. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds.

For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover. Also for purposes of this invention, the term "hydrocarbon" is contemplated to include all permissible compounds having at least one hydrogen and one carbon atom. In a broad aspect, the permissible hydrocarbons include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic organic compounds which can be substituted or unsubstituted.

The phrase "protecting group" as used herein means temporary substituents which protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones, respectively. The field of protecting group chemistry has been reviewed (Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991).

The term "ED_{50}" means the dose of a drug which produces 50% of its maximum response or effect. Alternatively, the dose which produces a pre-determined response in 50% of test subjects or preparations.

The term "LD_{50}" means the dose of a drug which is lethal in 50% of test subjects.

The term "therapeutic index" refers to the therapeutic index of a drug defined as LD_{50}/ED_{50}.

The term "structure-activity relationship (SAR)" refers to the way in which altering the molecular structure of drugs alters their interaction with a receptor, enzyme, etc.

The term "agonist" refers to a compound that mimics the action of natural transmitter or, when the natural transmitter is not known, causes changes at the receptor complex in the absence of other receptor ligands.

The term "antagonist" refers to a compound that binds to a receptor site, but does not cause any physiological changes unless another receptor ligand is present.

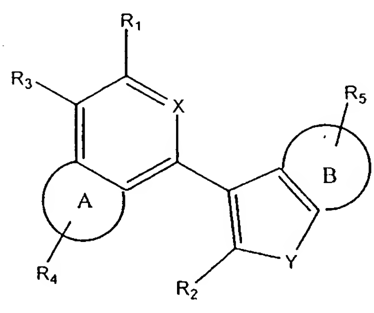
The term "competitive antagonist" refers to a compound that binds to a receptor site; its effects can be overcome by increased concentration of the agonist.

The term "partial agonist" refers to a compound that binds to a receptor site but does not produce the maximal effect regardless of its concentration.

The term "ligand" refers to a compound that binds at the receptor site.

II. Compounds of the Invention.

As set out above, the present invention makes available a novel class of compounds represented by general formula **1**.



1

Certain of the subject compounds can be classified on the basis of whether or not R_1 comprises a primary or secondary amine functional group. Merely for ease of reading, the application refers to "Class A" compounds, comprising a primary or secondary amine in R_1, and "Class B" compounds, which lack a primary or secondary amine in R_1. The presence of the amine in R_1, as demonstrated below in Example 31, can be correlated with the potency of the related quinoline-indole compounds against *Enterococci*.

Class A Compounds

In certain embodiments, the subject compounds are represented by the general formula 1, A, B, X, Y, R, R_2, R_3, R_4, R_5 being defined above, and R_1 representing alkyl(NHR), -C(Z)N(R)(R'-NHR), -C(Z)O(R'-NHR), -$S(Z)_2N(R)$(R'-NHR), or -$P(Z)_2N(R)$(R'-NHR), wherein Z independently for each occurrence represents $(R)_2$, O, S, or NR, and R' represents a covalent linker connecting the two nitrogens explicitly depicted above in the definitions of R_1; R' preferably being an alkyl, e.g., preferably a cyclic, branched or straight chain aliphatic group of 2-10 bonds in length, cycloalkyl, alkenyls, cycloalkenyl, alkynyl, aryl, heteroalkyl, or heteroaryl moiety.

In a preferred embodiment, X is N and Y is NR. Where Y represents NR, that occurrence of R is preferably H, alkyl, alkylsulfonyl, arylsulfonyl, or -$(CH_2)_m$-R_{80}, wherein R_{80} represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle, and m is an integer in the range 0 to 8 inclusive.

In more preferred embodiments, the subject compounds are represented by the general formula 1, substituents A, B, X, Y, and R being defined above:

wherein

R_1 represents alkyl(NHR), -C(Z)N(R)(R'-NHR), -C(Z)O(R'-NHR), -$S(Z)_2N(R)$(R'-NHR), or -$P(Z)_2N(R)$(R'-NHR), wherein Z independently for each occurrence represents $(R)_2$, O, S, or NR;

R' represents a covalent linker, preferably an alkyl, e.g., more preferably a cyclic, branched or straight chain aliphatic group of 2-10 bonds in length, cycloalkyl, alkenyls, cycloalkenyl, alkynyl, aryl, heteroalkyl, or heteroaryl moiety;

R_2 and R_3, independently for each occurrence, represent H or a hydrophobic aliphatic group, and more preferably R_2 and R_3 represent H, C_1-C_6 alkyl, or aryl, and even more preferably H or -CH_3;

R_4 independently for each occurrence represents C_1-C_6 alkyl, 1-alkenyl, 1-alkynyl, aryl, heteroalkyl, heteroaryl, -OR, -OCF_3, -$OC(R)_2OR$, -$C(R)_2OR$, or a small hydrophobic moiety (e.g. a halogen or halogenated alkyl), though preferably R_4 is a halogen, trihalogenated methyl, or -CCR_{60} (R_{60} being described below) and more preferably R_4 is a halogen, trihalogenated methyl; and

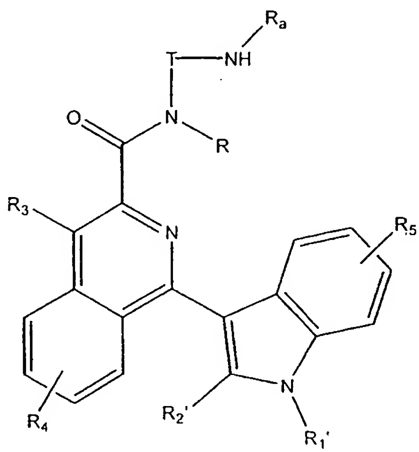
R_5 independently for each occurrence represents a small hydrophobic moiety (e.g. preferably a halogen or a halogenated alkyl, such as a trihalogenated methyl such as -CF_3).

In preferred embodiments of the compounds of class A, the above general definitions apply, and B is substituted at least once by R_5.

In preferred embodiments of the compounds of class A, the above general definitions apply, and at least one of R_2 or R_3 is alkyl or aryl.

In preferred embodiments of the compounds of class A, the above definitions apply, and R_1 represents alkyl(NHR), -C(Z)N(R)(R'-NHR), -S(Z)$_2$N(R)(R'-NHR), or -P(Z)$_2$N(R)(R'-NHR).

In more preferred embodiments of this class of compounds, the subject antibacterial compounds are represented by general formula **2**:



2

wherein

R, R_a, R_3, R_1', and R_2', for each occurrence, independently represent hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or -$(CH_2)_m$-R_{80};

R_4, and R_5, for each occurrence, independently represent halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or -$(CH_2)_m$-R_{80};

T represents a covalent linker, preferably being an alkyl, e.g., preferably a cyclic, branched or straight chain aliphatic group of 2-10 bonds in length, cycloalkyl, alkenyls, cycloalkenyl, alkynyl, aryl, heteroalkyl, or heteroaryl moiety;

the B-rings of the 1-isoquinolinyl and 3-indolyl moieties may be unsubstituted or substituted between one and four times inclusive by R_4 and R_5, respectively;

R_{80} represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

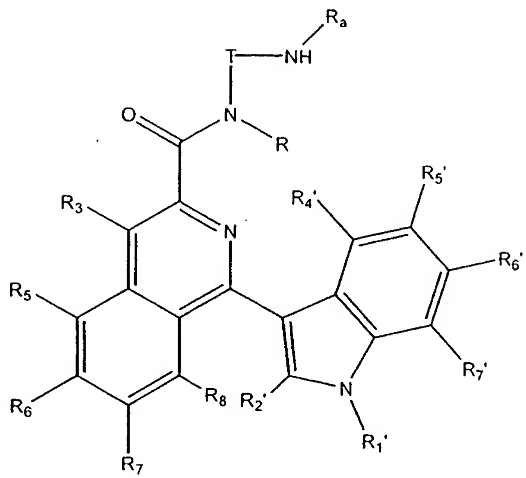
In preferred embodiments of the compounds of formula **2**:

R_2' and R_3 independently for each occurrence represent H or a hydrophobic aliphatic group, and more preferably R_2' and R_3 represent H, C_1-C_6 alkyl, or aryl, and even more preferably H or $-CH_3$;

R_4 independently for each occurrence represents C_1-C_6 alkyl, 1-alkenyl, 1-alkynyl, aryl, -OR, $-OCF_3$, $-OC(R)_2OR$, $-C(R)_2OR$, or a small hydrophobic moiety (e.g. a halogen or halogenated alkyl), preferably R_4 is a halogen, trihalogenated methyl or $-CCR_{60}$ (R_{60} being described below), and more preferably R_4 is a halogen or trihalogenated methyl; and

R_5 independently for each occurrence represents a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl such as a trihalogenated methyl).

In more preferred embodiments of this class of compounds, the subject antibacterial compounds are represented by the general formula below:



wherein

R, R_a, R_3, R_5, R_6, R_7, R_8, R_1', R_2', R_4', R_5', R_6', and R_7', for each occurrence, independently represent hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

T represents a covalent linker, preferably being an alkyl, e.g., preferably a cyclic, branched or straight chain aliphatic group of 2-10 bonds in length, cycloalkyl, alkenyls, cycloalkenyl, alkynyl, aryl, heteroalkyl, or heteroaryl moiety;

R_{80} represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

In preferred embodiments of the compounds represented above:

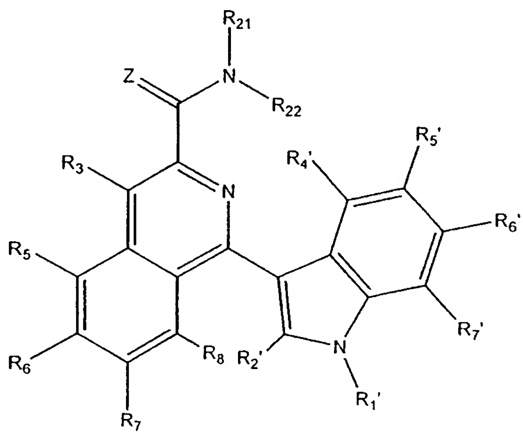
R_2' and R_3 independently for each occurrence represent H or a hydrophobic aliphatic group, and more preferably R_2' and R_3 represent H, C_1-C_6 alkyl, or aryl, and even more preferably H or $-CH_3$;

R_5, R_6, R_7, and R_8 independently for each occurrence represent H, C_1-C_6 alkyl, 1-alkenyl, 1-alkynyl, aryl, -OR, $-OCF_3$, $-OC(R)_2OR$, $-C(R)_2OR$, or a small hydrophobic moiety (e.g. a

halogen or halogenated alkyl), and more preferably they are selected from the group comprising halogen, trihalogenated methyl or -CCR$_{60}$ (R$_{60}$ being described below); and

R_4', R_5', R_6', and R_7' represent, independently for each occurrence, H, a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl such as a trihalogenated methyl).

In more preferred embodiments, the subject antibacterial compounds are represented by the following general formula:



wherein

Z represents O or $(R)_2$;

R, R_3, R_5, R_6, R_7, R_8, R_{21}, R_{22}, R_1', R_2', R_4', R_5', R_6', and R_7', for each occurrence, independently represent hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

R_{80} represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

In preferred embodiments, Z represents O or $(R)_2$;

R is as defined above;

R_2' and R_3, independently for each occurrence, represent H or a hydrophobic aliphatic group, and more preferably R_2' and R_3 represent H, C_1-C_6 alkyl, or aryl, and even more preferably H or $-CH_3$;

R_5, R_6, R_7 and R_8 independently for each occurrence represent H, C_1-C_6 alkyl, 1-alkenyl, 1-alkynyl, aryl, -OR, $-OCF_3$, $-OC(R)_2OR$, $-C(R)_2OR$, or a small hydrophobic moiety (e.g. a halogen or halogenated alkyl), and more preferably R_5, R_6, R_7 and R_8 each represent a halogen, trihalogenated methyl or $-CCR_{60}$ (R_{60} being described below);

R_1' represents H, alkyl, *p*-toluenesulfonyl, $-(CH_2)_nN(Phth)$, or $-(CH_2)_nN(R)_2$ wherein n is an integer in the range 1 to 6 inclusive;

R_4', R_5', R_6' and R_7' independently for each occurrence represent H, or a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl, such as a trihalogenated methyl); and

$N(R_{21})R_{22}$ taken together represents a heterocycle comprising from 4 to 8 members inclusive; or R_{21} and R_{22} independently for each occurrence represent H, alkyl, heteroalkyl, aryl, heteroaryl, or $-(CH_2)_m-R_{80}$, though more preferably $-(CH_2)_nNH(R_1')$, wherein n is an integer in the range 1 to 6 inclusive, or *ortho*-, *meta*-, or *para*-$CH_2C_6H_4CH_2NH(R_1')$, or 2-, 3-, or 4-((R$_1$')aminomethyl)cyclohexylmethyl, or 2-, 3-, or 4-((R$_1$')amino)cyclohexyl; with the proviso that R_{21} and R_{22} are selected such that $N(R_{21})R_{22}$ comprises a primary or secondary amine.

The preferred subclass of compounds described above is predicted to comprise compounds with minimum inhibitory concentrations (MICs) below 25 μg/mL against certain Gram-positive bacteria, especially methicillin-resistant *Staphylococcus aureus*, ciprofloxacin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* spp., and/or *Streptococcus pneumoniae*. Additionally, individual members of the preferred subclass of compounds described above should have MIC values less than 7 μg/mL or even less than 1 μg/mL against such bacteria.

Class B Compounds

The absence of a primary or secondary amine in the substituent at the 3-position of the isoquinolinyl moiety in general structure **2** is expected, based on the activity profile of the corresponding quinoline-indole family of compounds, to be tolerated with respect to maintenance of activity against MRSA, CRSA, and PRP. Other suitable groups could be selected to increase the polarity and/or stability of the resulting compounds. Thus, in yet other embodiments, the subject compounds are represented by the general formula **1**, A, B, X, Y, R, R_2, R_3, R_4, R_5 being defined in the general formula above, and R_1 representing H, Me, lower alkyl, halogen, -C(Z)OR, $-C(Z)N(R)_2$, $-S(Z)_2N(R)_2$, or $-P(Z)_2N(R)_2$, wherein Z independently for each occurrence represents $(R)_2$, O, S, or NR.

In a preferred embodiment, X is N and Y is NR. For those embodiments wherein Y represents NR, that occurrence of R is preferably H, alkyl, alkylsulfonyl, arylsulfonyl, or $-(CH_2)_m-R_{80}$, wherein R_{80} represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle, and m is an integer in the range 0 to 8 inclusive.

In certain preferred embodiments, R_1 represents hygrogen or halogen, X represents N, Y represents NH or NCH_3, R_2 and R_3 each independently represent H, lower alkyl, or aryl, A and B each represent fused benzo rings.

In preferred embodiments of the compounds of class B, the above definitions apply, and B is substituted at least once by an R_5.

In preferred embodiments of the compounds of class B, the above definitions apply, and at least one of R_2 or R_3 is alkyl or aryl.

In more preferred embodiments, the subject compounds are represented by the general formula **1**, A, B, X, Y, and R being generally defined above:

wherein

R_1 represents H, Me, lower alkyl, halogen, $-C(Z)OR$, $-C(Z)N(R)_2$, $-S(Z)_2N(R)_2$, or $-P(Z)_2N(R)_2$;

Z independently for each occurrence represents $(R)_2$, or O;

R_2 and R_3 independently for each occurrence represent H or a hydrophobic aliphatic group, and more preferably R_2 and R_3 represent H, C_1-C_6 alkyl, or aryl, and even more preferably H or $-CH_3$;

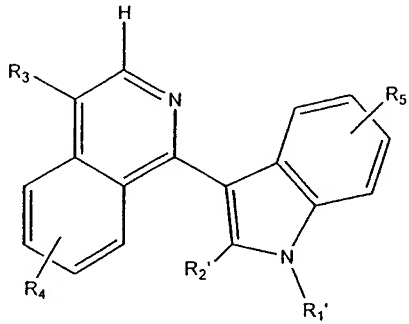
R_4 independently for each occurrence represents C_1-C_6 alkyl, 1-alkenyl, 1-alkynyl, aryl, $-OR$, $-OCF_3$, $-OC(R)_2OR$, $-C(R)_2OR$, or a small hydrophobic moiety (e.g. a halogen or halogenated alkyl), and more preferably R_4 is a halogen, trihalogenated methyl or $-CCR_{60}$ (R_{60} being described below); and

R_5 independently for each occurrence represents a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl, especially a trihalogenated methyl), $-C(O)N(R)_2$, $-CN$, $-NO_2$, $-OH$, $-OR$, $-O_2C$-aryl, or $-O_2C$-alkyl.

In further preferred embodiments, the above description applies wherein R_1 represents H, halogen, Me, lower alkyl, $-C(Z)N(R)_2$, $-S(Z)_2N(R)_2$, or $-P(Z)_2N(R)_2$.

In another preferred embodiment, the subject compounds are represented by **1**, wherein X represents N; Y represents NH or NMe; R_2 and R_3 each independently represent H; A and B each independently represent a fused benzo ring; and R_5 is present at least once.

In certain preferred embodiments, the subject antibacterial compounds are represented by general formula 3:



3

wherein

R_3, R_1', and R_2', for each occurrence, independently represent hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine. carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

R_4, and R_5, for each occurrence, independently represent halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

the B-rings of the 1-isoquinolinyl and 3-indolyl moieties may be unsubstituted or substituted between one and four times inclusive by R_4 and R_5, respectively;

R_{80} represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle , or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

In more preferred embodiments of the compounds of formula 3:

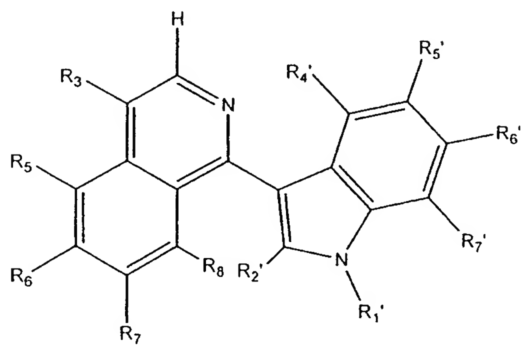
R_1' represents H, alkyl, *p*-toluenesulfonyl, $-(CH_2)_nN(Phth)$, or $-(CH_2)_nN(R)_2$; wherein n is an integer in the range 1 to 6 inclusive;

R_2'and R_3 independently for each occurrence represent H or a hydrophobic aliphatic group, and more preferably R_2' and R_3 represent H, C_1-C_6 alkyl, or aryl, and even more preferably H or $-CH_3$;

R_4 independently for each occurrence represents C_1-C_6 alkyl, 1-alkenyl, 1-alkynyl, aryl, -OR, $-OCF_3$, $-OC(R)_2OR$, $-C(R)_2OR$, or a small hydrophobic moiety (e.g. a halogen or halogenated alkyl), and more preferably R_4 represents a halogen, trihalogenated methyl or CCR_{60} (R_{60} being described below); and

R_5 independently for each occurrence represents a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl, especially a trihalogenated methyl), $-C(O)N(R)_2$, -CN, $-NO_2$, -OH, -OR, $-O_2Caryl$, or $-O_2Calkyl$.

In more preferred embodiments, the subject antibacterial compounds are represented by the following general formula:



wherein

R_1' represents H, alkyl, *p*-toluenesulfonyl, $-(CH_2)_nN(Phth)$, or $-(CH_2)_nN(R)_2$; wherein n is an integer in the range 1 to 6 inclusive;

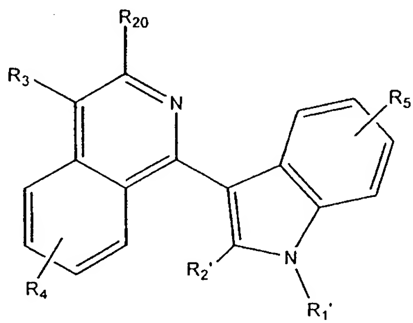
R_2' and R_3 independently for each occurrence represent H, C_1-C_6 alkyl, or aryl;

R_5, R_6, R_7, and R_8 independently for each occurrence represent H, C_1-C_6 alkyl, 1-alkenyl, 1-alkynyl, aryl, $-C(O)N(R)_2$, or a small hydrophobic moiety (e.g. a halogen or halogenated alkyl, preferaby a halogen or trihalogenated methyl); and

R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a small hydrophobic moiety (e.g. a halogen or halogenated alkyl, preferably a halogen or trihalogenated methyl), $-C(O)NR_2$, -CN, $-NO_2$, -OH, -OR, $-O_2Caryl$, or $-O_2Calkyl$.

The preferred subclass of compounds described above is predicted to comprise compounds with minimum inhibitory concentrations (MICs) below 25 μg/mL against certain Gram-positive bacteria, especially methicillin-resistant *Staphylococcus aureus*, ciprofloxacin-resistant *Staphylococcus aureus*, and/or *Streptococcus pneumoniae*. In more preferred embodiments, members of this subclass of compounds should have MIC values less than 7 μg/mL or even less than 1 μg/mL against such bacteria, particularly against methicillin-resistant *Staphylococcus aureus* and/or ciprofloxacin-resistant *Staphylococcus aureus*.

In preferred embodiments, the subject antibacterial compounds are represented by general formula 4:



4

wherein

R_{20} represents H, Me, lower alkyl, halogen, -C(Z)OR, -C(Z)N(R)$_2$, -S(Z)$_2$N(R)$_2$, or -P(Z)$_2$N(R)$_2$, wherein Z independently for each occurrence represents (R)$_2$, O, S, or NR;

R, R_3, R_1', and R_2', for each occurrence, independently represent hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or -$(CH_2)_m$-R_{80};

R_4, and R_5, for each occurrence, independently represent halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or -$(CH_2)_m$-R_{80};

the B-rings of the 1-isoquinolinyl and 3-indolyl moieties may be unsubstituted or substituted between one and four times inclusive by R_4 and R_5, respectively;

R_{80} represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle , or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

In preferred embodiments of the subject compounds **4**, the above general definitions apply, and R_5 is present at least once.

In preferred embodiments of the subject compounds **4**, the above general definitions apply, and at least one of R_2 or R_3 is alkyl or aryl.

In preferred embodiments of the compounds **4**, the above definitions apply, and R_{20} represents $-C(Z)N(R)_2$, $-S(Z)_2N(R)_2$, or $-P(Z)_2N(R)_2$.

In preferred embodiments of the compounds **4**, the above definitions apply, and R_{20} represents halogen.

In certain preferred embodiements, the subject antibacterial compounds are represented by general formula **4**, wherein

R_{20} represents fluorine, chlorine, bromine, or iodine;

R_1' represents H, alkyl, *p*-toluenesulfonyl, $-(CH_2)_nN(Phth)$, or $-(CH_2)_nN(R)_2$ wherein n is an integer in the range 1 to 6 inclusive;

R_2' and R_3 independently for each occurrence represent H, Me, C_1-C_6 alkyl, or aryl;

the B-rings of the 1-isoquinolinyl and 3-indolyl moieties may be unsubstituted or substituted between one and four times inclusive by R_4 and R_5, respectively;

R_4 independently for each occurrence represents Me, C_1-C_6 alkyl, 1-alkenyl, 1-alkynyl, aryl, -OR, $-OCF_3$, $-OCR_2OR$, $-CR_2OR$, or a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl, preferably a trihalogenated methyl); and

R_5 independently for each occurrence represents a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl, preferably a trihalogenated methyl), -CN, $-NO_2$, -OH, -OR, -O_2Caryl, or -O_2Calkyl.

In more preferred embodiments, the above definitions apply, and R_{20} is chlorine.

More preferably, the subject antibacterial compounds are represented by general formula **4**, wherein

R_{20} represents H, Me, lower alkyl, halogen, $-C(Z)OR$, $-C(Z)N(R)_2$, $-S(Z)_2N(R)_2$, or $-P(Z)_2N(R)_2$, wherein Z independently for each occurrence represents $(R)_2$, O, S, or NR;

R_1' represents H, alkyl, *p*-toluenesulfonyl, $-(CH_2)_nN(Phth)$, or $-(CH_2)_nN(R)_2$ wherein n is an integer in the range 1 to 6 inclusive;

R_2' and R_3 independently for each occurrence represent H, Me, C_1-C_6 alkyl, or aryl;

the B-rings of the 1-isoquinolinyl and 3-indolyl moieties may be unsubstituted or substituted between one and four times inclusive by R_4 and R_5, respectively;

R_4 independently for each occurrence represents Me, C_1-C_6 alkyl, 1-alkenyl, 1-alkynyl, aryl, -OR, $-OCF_3$, $-OCR_2OR$, $-CR_2OR$, or a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl, preferably a trihalogenated methyl); and

R_5 independently for each occurrence represents a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl, preferably a trihalogenated methyl), -CN, $-NO_2$, -OH, -OR, -O_2Caryl, or -O_2Calkyl.

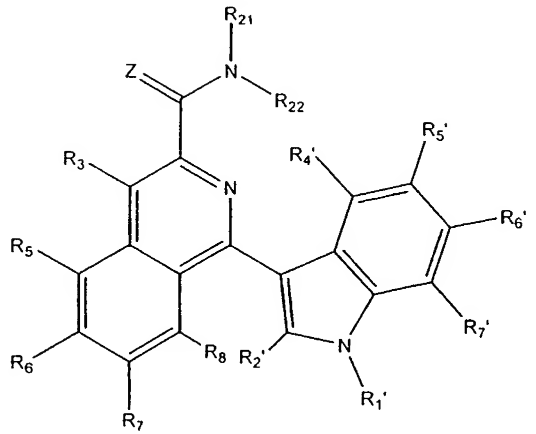
In preferred embodiments of the subject compounds, the above general definitions apply, and R_5 is present at least once.

In preferred embodiments of the subject compounds, the above general definitions apply, and at least one of R_2 or R_3 is alkyl or aryl.

In still further preferred embodiments, the subject antibacterial compounds are represented by general formula **4** and the preceding definitions, and R_{20} represents H, Me, lower alkyl, halogen, $-C(Z)N(R)_2$, $-S(Z)_2N(R)_2$, or $-P(Z)_2N(R)_2$, wherein Z independently for each occurrence represents $(R)_2$, O, S, or NR.

In further preferred embodiments, the above descriptions based on **4** apply wherein R_{20} represents H, Me, lower alkyl, halogen, $-C(Z)OR$, $-C(Z)N(R)_2$, $-S(Z)_2N(R)_2$, or $-P(Z)_2N(R)_2$, wherein Z independently for each occurrence represents $(R)_2$, O, S, or NR; and R_5 is present at least once.

In additional preferred embodiments, the subject antibacterial compounds are represented by the following general formula:



wherein

Z represents O or $(R)_2$;

R_2' and R_3 independently for each occurrence represent H or a hydrophobic aliphatic group, and more preferably R_2' and R_3 represent H, C_1-C_6 alkyl, or aryl, and even more preferably H or $-CH_3$;

R_5, R_6, R_7 and R_8 independently for each occurrence represent H, C_1-C_6 alkyl, 1-alkenyl, 1-alkynyl, aryl, -OR, $-OCF_3$, $-OC(R)_2OR$, $-C(R)_2OR$, or a small hydrophobic moiety (e.g. a halogen or halogenated alkyl), and more preferably R_5, R_6, R_7 and R_8 represent H, halogen, trihalogenated methyl, or $-CCR_{60}$ (R_{60} being described below);

R_1' represents H, alkyl, aryl, *p*-toluenesulfonyl, $-(CH_2)_nN(Phth)$, or $-(CH_2)_nN(R)_2$; wherein n is an integer in the range 1 to 6 inclusive;

R_4', R_5', R_6' and R_7' independently for each occurrence represent H, or a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl, especially a trihalogenated methyl); and

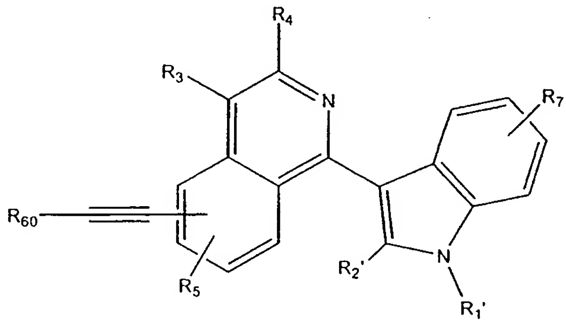
R_{21} and R_{22} independently for each occurrence represent H, alkyl, heteroalkyl, aryl, heteroaryl, *ortho*-, *meta*-, or *para*-$CH_2C_6H_4O(R_1')$, *ortho*-, *meta*-, or *para*-$CH_2C_6H_4OMe$, *ortho*-, *meta*-, or *para*-$CH_2C_6H_4OH$, (2-benzimidazolyl)CH_2-, 2-, 3-, or 4-methoxyphenyl, 2-, 3-, or 4-hydroxyphenyl, or 2-, 3-, or 4-$((R_1')_2NCH_2)$cyclohexylmethyl, or 2-, 3-, or 4-$((R_1')_2N)$cyclohexyl; or $N(R_{21})R_{22}$ taken together represents a heterocycle comprising from 4 to 8 members inclusive; with the proviso that, regardless of the specific identity of $N(R_{21})R_{22}$, it does not comprise a primary or secondary amine.

The preferred subclass of compounds described above is predicted to comprise compounds with minimum inhibitory concentrations (MICs) below 25 μg/mL against certain

Gram-positive bacteria, especially methicillin-resistant *Staphylococcus aureus*, ciprofloxacin-resistant *Staphylococcus aureus*, and/or *Streptococcus pneumoniae*. Additionally, individual members of the preferred subclass of compounds described above should have MICs less than 7 μg/mL or even less than 1 μg/mL against such bacteria.

Alkynyl-substituted

In still other embodiments, the subject antibacterial compounds are represented by the following general formula:



wherein

R_3, R_4, R_1', R_2', and R_{60} for each occurrence, independently represent hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

R_5, and R_7, for each occurrence, independently represent halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

the B-ring of the 1-isoquinolinyl moiety may be unsubstituted beyond the alkynyl group or substituted between one and three times inclusive by R_5;

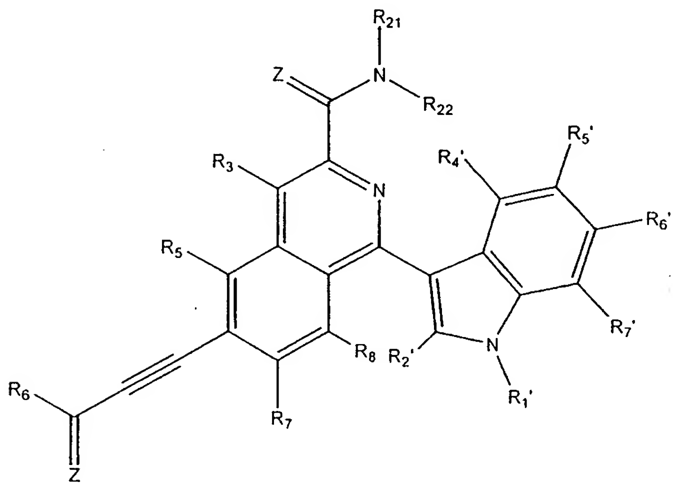
the B-ring of the 3-indolyl moiety may be unsubstituted or substituted between one and four times inclusive by R_7;

R_{80} represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle , or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

In preferred embodiments, R_{60} represents alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, or -C(Z)-R_6; where R_6 is selected from the group comprising NHR, $N(R)_2$, 1-piperidyl, 1-piperazinyl, 1-pyrrolidinyl, 2-phenylethylamino, 4-morpholinyl, and 4-phenylmethyl-1-piperidyl; Z independently for each occurrence represents $(R)_2$, O, S, or NR; and R is H or a lower alkyl.

In more preferred embodiments, the subject antibacterial compounds are represented by the following general formula:



wherein

Z independently for each occurrence represents $(R)_2$, O, S, or NR;

R_5, R_7, and R_8 independently for each occurrence represent H, Me, C_1-C_6 alkyl, heteroalkyl, 1-alkenyl, 1-alkynyl, aryl, heteroaryl, -OR, -OCF_3, -OCR_2OR, -CR_2OR, -CO_2R, or a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl, preferably a trihalogenated methyl);

R_6 is selected from the group comprising NHR, $N(R)_2$, 1-piperidyl, 1-piperazinyl, 1-pyrrolidinyl, 2-phenylethylamino, 4-morpholinyl, and 4-phenylmethyl-1-piperidyl;

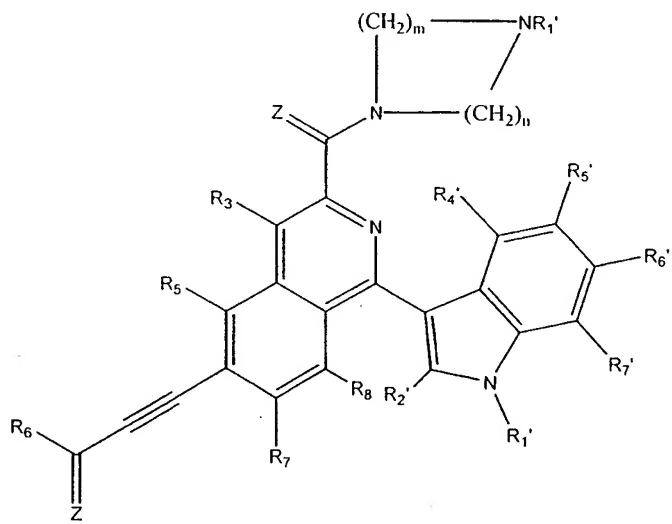
R_1' represents H, alkyl, aryl, *p*-toluenesulfonyl, -$(CH_2)_nN(Phth)$, or -$(CH_2)_nN(R)_2$; wherein n is an integer in the range 1 to 6 inclusive;

R_2' and R_3 independently for each occurrence represent H, Me, C_1-C_6 alkyl, or aryl;

R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl, preferably a trihalogenated methyl), $-C(O)NR_2$, $-CN$, $-NO_2$, $-OH$, $-OR$, $-O_2Caryl$, or $-O_2Calkyl$; and

R_{21} and R_{22} independently for each occurrence represent H, alkyl, heteroalkyl, aryl, heteroaryl, $-(CH_2)_m-R_{80}$, and more preferably $-(CH_2)_nN(R_1')_2$, wherein n is an integer in the range 1 to 6 inclusive, *ortho-*, *meta-*, or *para-*$CH_2C_6H_4CH_2N(R_1')_2$, *ortho-*, *meta-*, or *para-*$C_6H_4CH_2N(R_1')_2$, *ortho-*, *meta-*, or *para-*$CH_2C_6H_4O(R_1')$, *ortho-*, *meta-*, or *para-*$CH_2C_6H_4OMe$, *ortho-*, *meta-*, or *para-*$CH_2C_6H_4OH$, (2-benzimidazolyl)CH_2-, 2-, 3-, or 4-(R_1')Ophenyl, 2-, 3-, or 4-methoxyphenyl, 2-, 3-, or 4-hydroxyphenyl, or 2-, 3-, or 4-$((R_1')_2NCH_2)$cyclohexylmethyl, or 2-, 3-, or 4-$((R_1')_2N)$cyclohexylmethyl; or $N(R_{21})R_{22}$ taken together represent a heterocycle comprising from 4 to 8 members inclusive.

In additional preferred embodiments, the subject antibacterial compounds are represented by the following general formula:



wherein

Z independently for each occurrence represents $(R)_2$, O, S, or NR;

R_5, R_7, and R_8 independently for each occurrence represent H, Me, C_1-C_6 alkyl, heteroalkyl, 1-alkenyl, 1-alkynyl, aryl, heteroaryl, $-OR$, $-OCF_3$, $-OCR_2OR$, $-CR_2OR$, $-CO_2R$, or a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl, preferably a trihalogenated methyl);

R_6 is selected from the group comprising NHR, $N(R)_2$, 1-piperidyl, 1-piperazinyl, 1-pyrrolidinyl, 2-phenylethylamino, 4-morpholinyl, and 4-phenylmethyl-1-piperidyl;

R_1' represents H, alkyl, aryl, *p*-toluenesulfonyl, $-(CH_2)_nN(Phth)$, or $-(CH_2)_nN(R)_2$; wherein n is an integer in the range 1 to 6 inclusive;

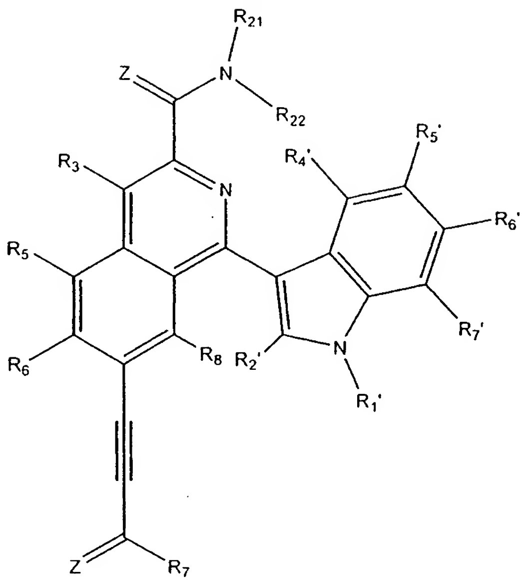
R_2' and R_3 independently for each occurrence represent H, Me, C_1-C_6 alkyl, or aryl;

R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl, preferably a trihalogenated methyl), $-C(O)NR_2$, -CN, $-NO_2$, -OH, -OR, $-O_2$Caryl, or $-O_2$Calkyl; and

m and n are integers independently selected from the range 1 to 4 inclusive.

The preferred subclasses of compounds described above is predicted to comprise compounds with minimum inhibitory concentrations (MICs) below 25 μg/mL against certain Gram-positive bacteria, especially methicillin-resistant *Staphylococcus aureus*, ciprofloxacin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* spp., or *Streptococcus pneumoniae*. Additionally, members of this subclass of compounds should have MIC values less than 7 μg/mL or even less than 1 μg/mL against such bacteria, particularly against methicillin- and/or ciprofloxacin-resistant *Staphylococcus aureus*.

In more preferred embodiments, the subject antibacterial compounds are represented by the following general formula:



wherein

Z independently for each occurrence represents $(R)_2$, O, S, or NR;

R_5, R_6, and R_8 independently for each occurrence represent H, Me, C_1-C_6 alkyl, heteroalkyl, 1-alkenyl, 1-alkynyl, aryl, heteroaryl, -OR, $-OCF_3$, $-OCR_2OR$, $-CR_2OR$, $-CO_2R$, or a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl, preferably a trihalogenated methyl);

R_7 is selected from the group comprising NHR, $N(R)_2$, 1-piperidyl, 1-piperazinyl, 1-pyrrolidinyl, 2-phenylethylamino, 4-morpholinyl, and 4-phenylmethyl-1-piperidyl;

R_1' represents H, alkyl, aryl, *p*-toluenesulfonyl, $-(CH_2)_nN(Phth)$, or $-(CH_2)_nN(R)_2$; wherein n is an integer in the range 1 to 6 inclusive;

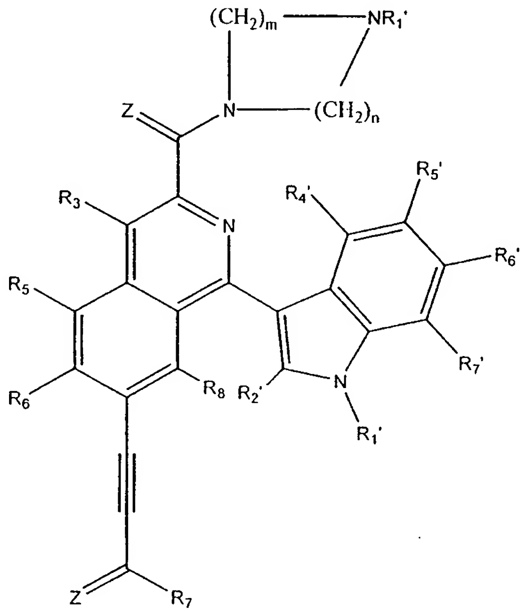
R_2' and R_3 independently for each occurrence represent H, Me, C_1-C_6 alkyl, or aryl;

R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl, preferably a trihalogenated methyl), $-C(O)NR_2$, -CN, $-NO_2$, -OH, -OR, $-O_2$Caryl, or $-O_2$Calkyl; and

R_{21} and R_{22} independently for each occurrence represent H, alkyl, heteroalkyl, aryl, heteroaryl, $-(CH_2)_m-R_{80}$, and more preferably $-(CH_2)_nN(R_1')_2$, wherein n is an integer in the range 1 to 6 inclusive, *ortho-*, *meta-*, or *para-*$CH_2C_6H_4CH_2N(R_1')_2$, *ortho-*, *meta-*, or *para-*$C_6H_4CH_2N(R_1')_2$, *ortho-*, *meta-*, or *para-*$CH_2C_6H_4O(R_1')$, *ortho-*, *meta-*, or *para-*$CH_2C_6H_4OMe$, *ortho-*, *meta-*, or *para-*$CH_2C_6H_4OH$, (2-benzimidazolyl)CH_2-, 2-, 3-, or 4-(R_1')Ophenyl, 2-, 3-, or 4-methoxyphenyl, 2-, 3-, or 4-hydroxyphenyl, or 2-, 3-, or 4-($(R_1')_2NCH_2$)cyclohexylmethyl,

or 2-, 3-, or 4-((R_1')$_2$N)cyclohexylmethyl; or $N(R_{21})R_{22}$ taken together represent a heterocycle comprising from 4 to 8 members inclusive.

In additional preferred embodiments, the subject antibacterial compounds are represented by the following general formula:



wherein

Z independently for each occurrence represents $(R)_2$, O, S, or NR;

R_5, R_6, and R_8 independently for each occurrence represent H, Me, C_1-C_6 alkyl, heteroalkyl, 1-alkenyl, 1-alkynyl, aryl, heteroaryl, -OR, -OCF_3, -OCR_2OR, -CR_2OR, -CO_2R, or a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl, preferably a trihalogenated methyl);

R_7 is selected from the group comprising NHR, $N(R)_2$, 1-piperidyl, 1-piperazinyl, 1-pyrrolidinyl, 2-phenylethylamino, 4-morpholinyl, and 4-phenylmethyl-1-piperidyl;

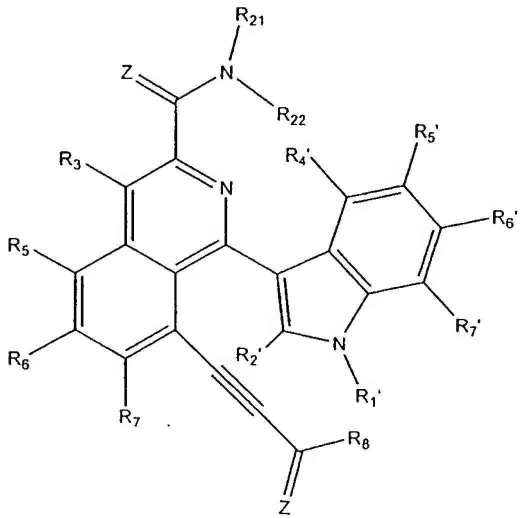
R_1' represents H, alkyl, aryl, *p*-toluenesulfonyl, -$(CH_2)_nN(Phth)$, or -$(CH_2)_nN(R)_2$ wherein n is an integer in the range 1 to 6 inclusive;

R_2' and R_3 independently for each occurrence represent H, Me, C_1-C_6 alkyl, or aryl;

R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl, preferably a trihalogenated methyl), -C(O)NR_2, -CN, -NO_2, -OH, -OR, -O_2Caryl, or -O_2Calkyl; and

m and n are integers independently selected from the range 1 to 4 inclusive.

In further preferred embodiments, the subject antibacterial compounds are represented by the following general formula:



wherein

Z independently for each occurrence represents $(R)_2$, O, S, or NR;

R_5, R_6, and R_7 independently for each occurrence represent H, Me, C_1-C_6 alkyl, heteroalkyl, 1-alkenyl, 1-alkynyl, aryl, heteroaryl, -OR, -OCF_3, -OCR_2OR, -CR_2OR, -CO_2R, or a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl, preferably a trihalogenated methyl);

R_8 is selected from the group comprising NHR, $N(R)_2$, 1-piperidyl, 1-piperazinyl, 1-pyrrolidinyl, 2-phenylethylamino, 4-morpholinyl, and 4-phenylmethyl-1-piperidyl;

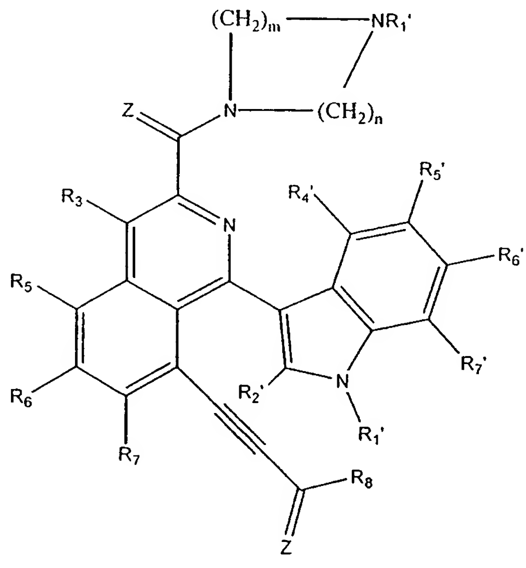
R_1' represents H, alkyl, aryl, *p*-toluenesulfonyl, -$(CH_2)_n$N(Phth), or -$(CH_2)_nN(R)_2$; wherein n is an integer in the range 1 to 6 inclusive;

R_2' and R_3 independently for each occurrence represent H, Me, C_1-C_6 alkyl, or aryl;

R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl, preferably a trihalogenated methyl), -C(O)NR_2, -CN, -NO_2, -OH, -OR, -O_2Caryl, or -O_2Calkyl; and

R_{21} and R_{22} independently for each occurrence represent H, alkyl, heteroalkyl, aryl, heteroaryl, -$(CH_2)_m$-R_{80}, and more preferably -$(CH_2)_nN(R_1')_2$, wherein n is an integer in the range 1 to 6 inclusive, *ortho-*, *meta-*, or *para*-$CH_2C_6H_4CH_2N(R_1')_2$, *ortho-*, *meta-*, or *para*-$C_6H_4CH_2N(R_1')_2$, *ortho-*, *meta-*, or *para*-$CH_2C_6H_4O(R_1')$, *ortho-*, *meta-*, or *para*-$CH_2C_6H_4OMe$, *ortho-*, *meta-*, or *para*-$CH_2C_6H_4OH$, (2-benzimidazolyl)CH_2-, 2-, 3-, or 4-(R_1')Ophenyl, 2-, 3-, or 4-methoxyphenyl, 2-, 3-, or 4-hydroxyphenyl, or 2-, 3-, or 4-((R_1')$_2$NCH$_2$)cyclohexylmethyl, or 2-, 3-, or 4-((R_1')$_2$N)cyclohexylmethyl; or $N(R_{21})R_{22}$ taken together represent a heterocycle comprising from 4 to 8 members inclusive.

In additional preferred embodiments, the subject antibacterial compounds are represented by the following general formula:



wherein

Z independently for each occurrence represents $(R)_2$, O, S, or NR;

R_5, R_6, and R_7 independently for each occurrence represent H, Me, C_1-C_6 alkyl, heteroalkyl, 1-alkenyl, 1-alkynyl, aryl, heteroaryl, -OR, -OCF_3, -OCR_2OR, -CR_2OR, -CO_2R, or a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl, preferably a trihalogenated methyl);

R_8 is selected from the group comprising NHR, $N(R)_2$, 1-piperidyl, 1-piperazinyl, 1-pyrrolidinyl, 2-phenylethylamino, 4-morpholinyl, and 4-phenylmethyl-1-piperidyl;

R_1' represents H, alkyl, aryl, *p*-toluenesulfonyl, $-(CH_2)_nN(Phth)$, or $-(CH_2)_nN(R)_2$; wherein n is an integer in the range 1 to 6 inclusive;

R_2' and R_3 independently for each occurrence represent H, Me, C_1-C_6 alkyl, or aryl;

R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a small hydrophobic moiety (e.g. a halogen or a halogenated alkyl, preferably a trihalogenated methyl), $-C(O)NR_2$, -CN, $-NO_2$, -OH, -OR, $-O_2$Caryl, or $-O_2$Calkyl; and

m and n are integers independently selected from the range 1 to 4 inclusive.

The antibacterial properties of the compounds of the present invention may be determined from a bacterial lysis assay, as well as by other methods, including, *inter alia*, growth inhibition assays (e.g., such as described by Blondelie et al. (1992) Biochemistry 31:12688), fluorescence-based bacterial viability assays (e.g., Molecular Probes BacLight), flow cytometry analyses (Arroyo et al. (1995) J. Virol. 69: 4095-4102), and other standard assays known to those skilled in the art.

The assays for growth inhibition of a microbial target can be used to derive an ED_{50} value for the compound, that is, the concentration of compound required to kill 50% of the microbial sample being tested.

Growth inhibition by an antimicrobial compound of the invention may also be characterized in terms of the minimum inhibitory concentration (MIC), which is the concentration of compound required to achieve inhibition of microbial cell growth. Such values are well known to those in the art as representative of the effectiveness of a particular antimicrobial agent (e.g., an antibiotic) against a particular organism or group of organisms. For instance, cytolysis of a bacterial population by an antimicrobial compound can also be characterized, as described above by the minimum inhibitory concentration, which is the concentration required to reduce the viable bacterial population by 99.9%. The value of MIC_{50} can also be used, defined as the concentration of a compound required to reduce the viable bacterial population by 50%. In preferred embodiments, the compounds of the present invention are selected for use based, *inter alia*, on having MIC values of less than 25 μg/mL, more preferably less than 7 μg/mL, and even more preferably less than 1 μg/mL against a desired bacterial target, e.g., a Gram positive bacteria' such as methicillin-resistant *Staphylococcus aureus*, ciprofloxacin-resistant *Staphylococcus aureus*, or *Streptococcus pneumoniae*.

Another parameter useful in identifying and measuring the effectiveness of the antimicrobial compounds of the invention is the determination of the kinetics of the antimicrobial activity of a compound. Such a determination can be made by determining

antimicrobial activity as a function of time. In a preferred embodiment, the compounds display kinetics which result in efficient lysis of a microorganism. In a preferred embodiment, the compounds are bacteriocidal.

Furthermore, the preferred antimicrobial compounds of the invention display selective toxicity to target microorganisms and minimal toxicity to mammalian cells. Determination of the toxic dose (or "LD_{50}") can be carried using protocols well known in the field of pharmacology. Ascertaining the effect of a compound of the invention on mammalian cells is preferably performed using tissue culture assays, e.g., the present compounds can be evaluated according to standard methods known to those skilled in that art (see for example Gootz, T. D. (1990) Clin. Microbiol. Rev. 3:13-31). For mammalian cells, such assay methods include, *inter alia*, trypan blue exclusion and MTT assays (Moore et al. (1994) Compound Research 7:265-269). Where a specific cell type may release a specific metabolite upon changes in membrane permeability, that specific metabolite may be assayed, e.g., the release of hemoglobin upon the lysis of red blood cells (Srinivas et al. (1992) J. Biol. Chem. 267:7121-7127). The compounds of the invention are preferably tested against primary cells, e.g., using human skin fibroblasts (HSF) or fetal equine kidney (FEK) cell cultures, or other primary cell cultures routinely used by those skilled in the art. Permanent cell lines may also be used, e.g., Jurkat cells. In preferred embodiments, the subject compounds are selected for use in animals, or animal cell/tissue culture based at least in part on having LD_{50}'s at least one order of magnitude greater than the MIC or ED_{50} as the case may be, and even more preferably at least two, three and even four orders of magnitude greater. That is, in preferred embodiments where the subject compounds are to be administered to an animal, a suitable therapeutic index is preferably greater than 10, and more preferably greater than 10, 1000 or even 10,000.

Antibacterial assays for the compounds of the invention can be performed to determine the bacterial activity toward both Gram-positive and Gram-negative microorganisms. Typical Gram-negative pathogens which may be sensitive to the antibacterial agents of the present invention can include, for example, species of genus Escherichia, genus Enterobacter, genus Klebsiella, genus Serratia, genus Proteus and genus Pseudomonas. For example, the subject compositions and methods can be used as part of treatment and prevention regimens for infections by some of the most frequently encountered Gram-negative and Gram-positive organisms, including those involving *Escherichia coli* (*E. Coli*), *Klebsiella peumoniae* (*K. peumoniae*), *Serratia marcescens*, *Enterobacter aerogenes* and *Enterobacter cloacae* (*E. aerogenes* and *E. cloacae*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Neisseria meningitidis* (*N. meningitidis*), Group B Streptococcus *aureus* and *Staphylococcus aureus*, *Streptococcus pneumonia*, *Streptococcus pyogenes*, *Corynebacter diphtheriae*, *Gardnierella vaginalis*, *Actinetobacter* spp., *Bordella pertussis*, *Haemophilus aegyptius*, *Haemophilus influenza*, *Haemophilus ducreyi*, Shigella spp, Serratia spp., and *Propionibacterium acnes*.

The above list of pathogens is purely illustrative and is in no way to be interpreted as restrictive.

Examples of conditions which can be treated include illnesses of the respiratory passages and of the pharyngeal cavity; otitis, pharyngitis, pneumonia, peritonitis, pyelonephritis, cystitus, endocarditis, systemic infections, bronchitis, arthritis, local inflammations, skin infections, conjuntivitus, and infections of any surgically created vascular access for the purpose of hemodialysis.

The antibiotics of the present invention can also be used prophylactically in animal breeding and livestock husbandry, and as an agents for promoting and accelerating growth and for improving feedstuff utilization in both healthy and sick animals.

In preferred embodiments, the antibacterial agents of the present invention are selected based on their ability to inhibit growth of Gram-positive bacteria. Such Gram-positive bacteria include bacteria from the following species: Staphylococcus, Streptococcus, Micrococcus, Peptococcus, Peptostreptococcus, Enterococcus, Bacillus, Clostridium, Lactobacillus, Listeria, Erysipelothrix, Propionibacterium, Eubacterium, and Corynebacterium.

A variety of Gram-positive organisms are capable of causing sepsis. The most common organisms involved in sepsis are *Staphylococcus aureus*, *Streptoccocus pneumoniae*, coagulase-negative staphylococci, beta-hemolytic streptococci, and enterococci, but any Gram-positive organism may be involved. (see, e.g., Bone, (1993) J. Critical Care 8:51-59). Thus, it is specifically contemplated that the subject compositions and methods can be used as part of a therapeutic treatment or prevention program for sepsis involving Gram-positive bacteria.

Accordingly, in one embodiment, *S. aureus* is used as a model of a Gram-positive microorganism in testing/selecting the compounds of the present invention. This bacteria is also a significant clinical target as well because it is refractive to most systemic antibiotic treatments. *Staphylococcus aureus* is the most frequent cause of skin, wound, and blood infections and the second most frequent cause of lower respiratory tract infections, and the microorganism tends to prey on immunocompromised and institutionalized patients. Thus, the subject compounds can be used to treat such infections caused by *Staphylococcus*, as well as in the treatment of conjunctivitis, outer ear infections and the like.

One of the key contributors to the increase in mortality and morbidity due to bacterial infections is the increasing prevalence of drug-resistant bacteria. Examples of the seriousness of antibiotic resistance are methicillin-resistant *S. aureus* (MRSA), ciprofloxacin-resistant *S. aureus* (CRSA), and the emergence of vancomycin-resistant *S. aureus* which have become resistant to virtually all currently used antibiotics. Thus, methicillin-resistant *S. aureus* may also be used as an antibiotic-resistant model organism for selecting the subject compounds. In a preferred embodiment, the antibacterial agents of the present invention can be used in the treatment and/or prevention of endocarditis, e.g., which may be caused by MRSA or CRSA.

The heavy use of vancomycin to treat MRSA infections has in turn contributed to the emergence of new strains of enterococci, the third most prevalent cause of bacterial infection in the U.S., which are resistant to vancomycin. Enterococcus causes as many as 15 percent of bacterial endocarditis cases; it is also the cause of meningitis, and infections in the urinary tract, stomach and intestines. Infections caused by these vancomycin-resistant enterococci (VRE) frequently do not respond to any current therapies, and in many cases prove fatal. Accordingly, the subject compounds can be selected using an assay based on *E. faecalis* sensitivity, and in particular, the vancomycin-resistant isolates found in clinical settings such as a hospital.

The subject compositions may also be selected for treatment of infection by Streptococcus. Streptococcus species are found associated in a great variety of pathologic conditions among which are gangrene, puerperal infections, subacute bacterial endocarditis, septic sore throat, rheumatic fever, and pneumonia. Agents which are active against Streptococcus species are, therefore, greatly needed.

To further illustrate, *E. coli* and *P. aeruginosa* are examples of Gram-negative organisms which may be sensitive to the subject antibacterial agents. *P. aeruginosa* is a particularly problematic source of disease in such conditions as lung infections in patients with cystic fibrosis, burn infections, eye and urinary tract infections, and infection with *P. aeruginosa* may result in serious septicemia. Moreover, imipenem-resistant *P. aeruginosa* are increasing in the clinical field. Enteropathogenic *E. coli* are responsible for outbreaks of diarrhea in infants and newborns, and diarrhea, including "traveler's diarrhea", in adults. *E. coli* may be invasive and toxin-producing, causing sometimes fatal infections, such as cystitis, pyelitis, pyelonephritis, appendicitis, peritonitis, gallbladder infection, septicemia, meningitis and endocarditis.

In still other embodiments, the subject compounds can be used in the treatment of infections caused by *Serratia spp.* For instance, *S. marcescens* is a source of ophthalmic and other topical infections, and can be readily provided in assays intended to identify those compounds of the present invention which are bactercidal at suitable concentrations against that bacteria.

The subject compounds may also be used in the treatment of external ear infections (otitis externa), or in the treatment of sexually transmitted diseases such as *Niesseria gonorrhea* and trichomonas infections.

Certain compounds according to the invention may also be selected on the basis of their activity against typical and atypical Mycobacteria and *Helicobacter pylori*, and also against bacteria-like microorganisms, such as, for example, Mycoplasma and Rickettsia. They are therefore particularly suitable in human and veterinary medicine for the prophylaxis and chemotherapy of local and systemic infections caused by these pathogens. *Mycobacterium boris*, like *M. tuberculosis*, *M. africanum*, *M. ulcerans*, and *M. leprae*, is a strict pathogen. *M.*

bovis is a significant pathogen throughout much of the world, causing tuberculosis, primarily in cattle.

In other embodiments, the subject compositions can be used in the treatment/prevention of infection by Salmonella. Salmonella spp. cause food poisoning, resulting in nausea, vomiting, diarrhea and sometimes-fatal septicemia. For instance, *S. typhi* is the etiological agent of typhoid fever.

The compositions and methods of the present invention may also be useful in the treatment of infection by Shigella. Shigella spp., including *S. dysenteriae*, are common waterborne pathogenic agents, causing bacillary dysentery as well as bacteremia and pneumonia. In the United States and Canada, *S. sonnei* and *S. flexneri* have become the most common etiological agents in bacillary dysentery.

Bacteria of the genus Yersinia are also pathogens which may be treated by the subject compositions. *Y. Enterocolitica*, for example, is an enteric pathogen. Infection with this microorganism causes severe diarrhea, gastroenteritis and other types of infections such as bacteremia, peritonitis, cholecystis, visceral abscesses, and mesenteric lymphadenitis. Septicemia with 50% mortality has been reported. *Y. pestis* is the etiologic agent of bubonic, pneumonic, and septicemic plague in humans.

The subject compositions can be used for sterilization of surfaces such as countertops, surgical instruments, bandages, and skin; as pharmaceutical compositions, including by way of example creams, lotions, ointments, or solutions for external application to skin and mucosal surfaces, including the cornea, dermal cuts and abrasions, burns, and sites of bacterial or fungal infection; as pharmaceutical compositions, including by way of example creams, lotions, ointments, emulsions, liposome dispersions, tablets, or solutions, for administration to internal mucosal surfaces such as the oral cavity or vagina to inhibit the growth of bacteria (or other microorganisms); and as pharmaceutical compositions such as creams, gels, or ointments for coating indwelling invasive devices such as intravenous lines and catheters and similar implants which are susceptible to harboring bacteria.

The subject compositions are also useful for sterilization of *in vitro* tissue and cell culture media.

The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given by forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc. administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral and topical administrations are preferred.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal,

intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticulare, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically-acceptable dosage forms such as described below or by other conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide prodrugs thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular antibacterial employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, intravenous, intracerebroventricular, subcutaneous, and topical doses of the compounds of this invention for a

patient, when used for the indicated antibacterial effects, will range from about 0.0001 to about 100 mg per kilogram of body weight per day.

If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

The term "treatment" is intended to encompass also prophylaxis, therapy and cure.

The patient receiving this treatment is any animal in need, including primates, and in particular humans, and other mammals such as equines, cattle, swine and sheep; and poultry and pets in general.

The compound of the invention can be administered as such or in admixtures with pharmaceutically acceptable carriers and can also be administered in conjunction with other antimicrobial agents such as penicillins, cephalosporins, aminoglycosides and glycopeptides. Conjunctive therapy, thus includes sequential, simultaneous and separate administration of the active compound in a way that the therapeutical effects of the first administered compound has not entirely disappeared when the subsequent compound is administered.

III. Pharmaceutical Compositions

While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical formulation (composition). The antibiotic compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics.

Thus, another aspect of the present invention provides pharmaceutically acceptable compositions comprising a therapeutically-effective amount of one or more of the compounds described above, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. As described in detail below, the pharmaceutical compositions of the present invention may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular or intravenous injection as, for example, a sterile solution or suspension; (3) topical application, for example, as a cream, ointment or spray applied to the skin; or (4) intravaginally or intrarectally, for example, as a pessary, cream or foam. However, in certain embodiments the subject compounds may be simply dissolved or suspended in sterile water.

The phrase "therapeutically-effective amount" as used herein means that amount of a compound, material, or composition comprising a compound of the present invention which is

effective for producing some desired therapeutic effect by inhibiting bacterial cell growth when administered to an animal, at a reasonable benefit/risk ratio applicable to any medical treatment.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject antibacterial agent from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

As set out above, certain embodiments of the present antibacterials may contain a basic functional group, such as amino or alkylamino, and are, thus, capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable acids. The term "pharmaceutically-acceptable salts" in this respect, refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19)

The pharmaceutically acceptable salts of the subject compounds include the conventional nontoxic salts or quaternary ammonium salts of the compounds, e.g., from non-toxic organic or inorganic acids. For example, such conventional nontoxic salts include those derived from inorganic acids such as hydrochloride, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicyclic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, and the like.

In other cases, the compounds of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable bases. The term "pharmaceutically-acceptable salts" in these instances refers to the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention. These salts can likewise be prepared *in situ* during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically-acceptable metal cation, with ammonia, or with a pharmaceutically-acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. (See, for example, Berge et al., *supra*)

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate, magnesium stearate, and polyethylene oxide-polypropylene oxide copolymer as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that

amount of the compound which produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 1 per cent to about ninety-nine percent of active ingredient, preferably from about 5 per cent to about 70 per cent, most preferably from about 10 per cent to about 30 per cent.

Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, sodium carbonate, and sodium starch glycolate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol, glycerol monostearate, and polyethylene oxide-polypropylene oxide copolymer; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or

dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Additionally, cyclodextrins, e.g. hydroxypropyl-β-cyclodextrin, may be used to solubilize compounds.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate,

and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active antibacterial.

Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically-acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the antibacterial in the proper medium. Absorption enhancers can also be used to increase the flux of the antibacterial across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable

oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. Because solutions are particularly important for intravenous administration, solubilizing agents, e.g. cyclodextrins, can be used.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. One strategy for depot injections includes the use of polyethylene oxide-polypropylene oxide copolymers wherein the vehicle is fluid at room temperature and solidifies at body temperature.

Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

When the compounds of the present invention are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

The addition of the active compound of the invention to animal feed is preferably accomplished by preparing an appropriate feed premix containing the active compound in an effective amount and incorporating the premix into the complete ration.

Alternatively, an intermediate concentrate or feed supplement containing the active ingredient can be blended into the feed. The way in which such feed premixes and complete rations can be prepared and administered are described in reference books (such as "Applied

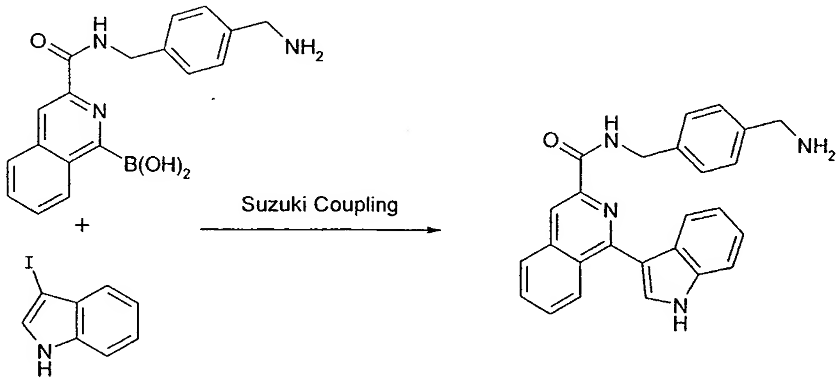
Animal Nutrition", W.H. Freedman and CO., San Francisco, U.S.A., 1969 or "Livestock Feeds and Feeding" O and B books, Corvallis, Ore., U.S.A., 1977).

The compounds covered in this invention may be administered alone or in combination with other antibacterial agents or in combination with a pharmaceutically acceptable carrier of dilutent. The compounds of the invention may be administered intravenously, intramuscularly, intraperitoneally, subcutaneously, topically, orally, or by other acceptable means. The compounds may be used to treat bacterial infections in mammals (i.e., humans, livestock, and domestic animals), birds, lizards, and any other organism which can tolerate the compounds, and also to inhibit bacterial growth in cell culture. The compounds can also be used for effects related to their antibacterial activity such as for increasing the weight gain of livestock.

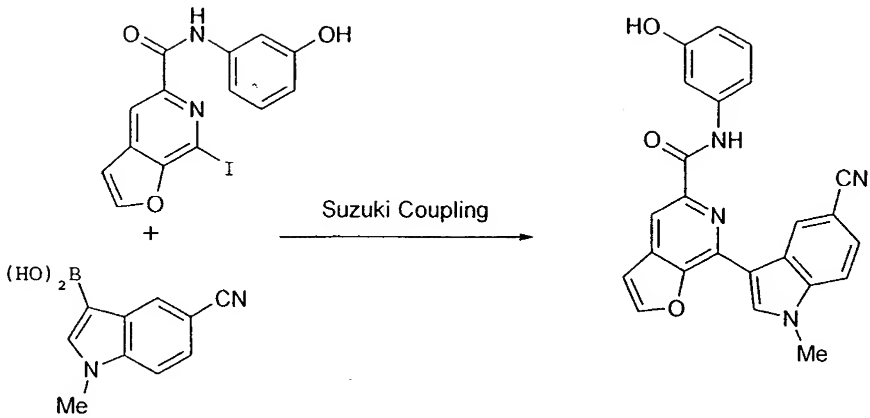
IV. Synthetic Schemes

The subject isoquinoline-indoles, and congeners thereof, can be prepared readily from individual heterocyclic components by employing the cross-coupling technologies of Suzuki, Stille, and the like. These coupling reactions are carried out under relatively mild conditions and tolerate a wide range of "spectator" functionality. A number of illustrative examples are shown below.

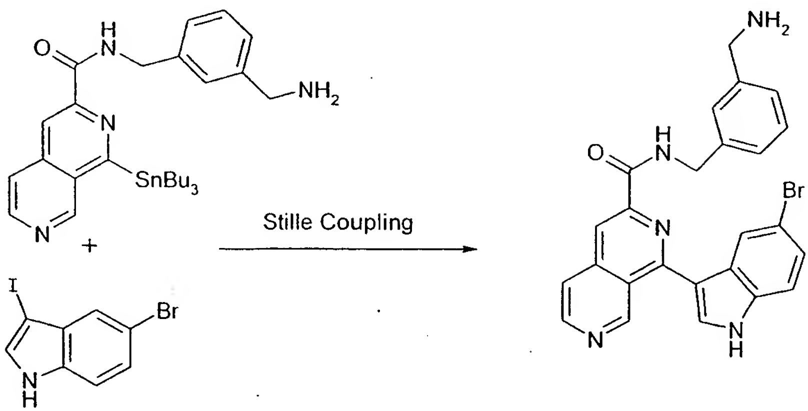
a. Illustrative Suzuki Coupling #1



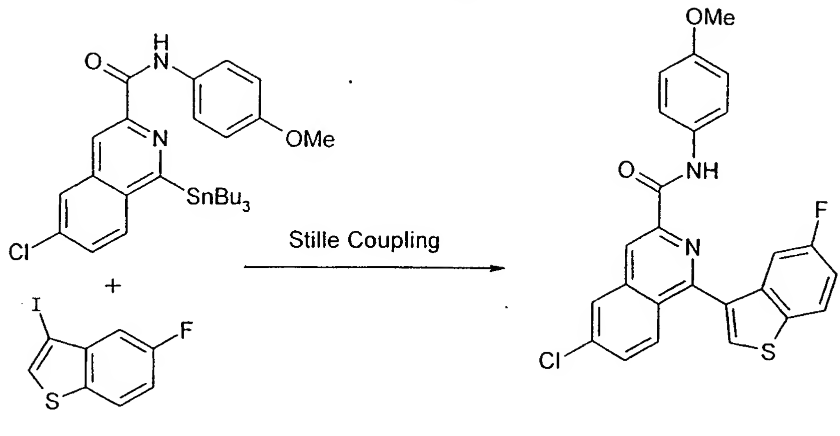
b. Illustrative Suzuki Coupling #2



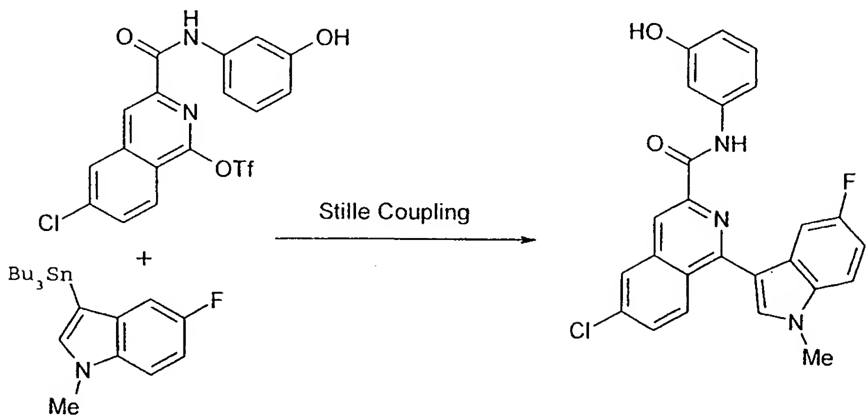
c. Illustrative Stille Coupling #1



d. Illustrative Stille Coupling #2

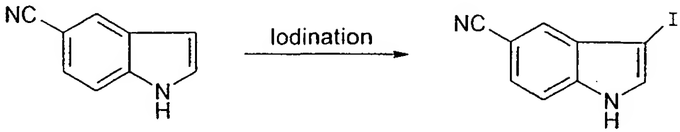


e. Illustrative Stille Coupling #3

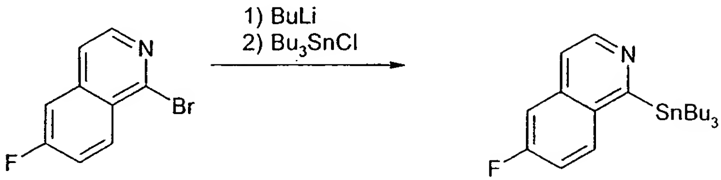


Members of the general classes of coupling substrates outlined above -- arylstannanes, arylboronic acids, aryl triflates and aryl halides -- are available from the parent heterocycles. In general, the transformations required to prepare a coupling substrate are reliable and amenable to scale-up. Illustrative examples are shown below.

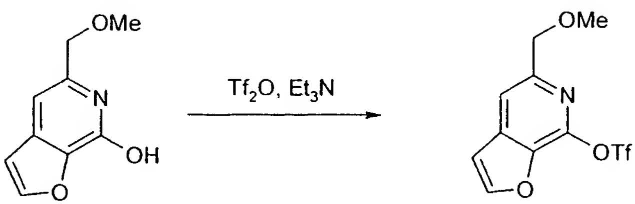
f. Illustrative Preparation of a 3-Iodoindole



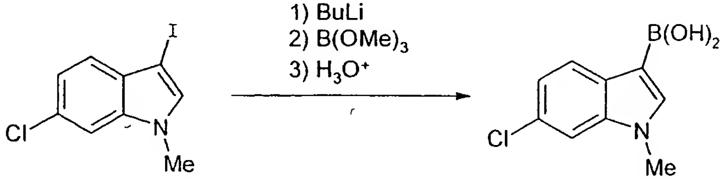
g. Illustrative Preparation of a 1-(Tributylstannyl)isoquinoline



h. Illustrative Preparation of a 2-(Trifluoromethanesulfonyloxy)pyridine

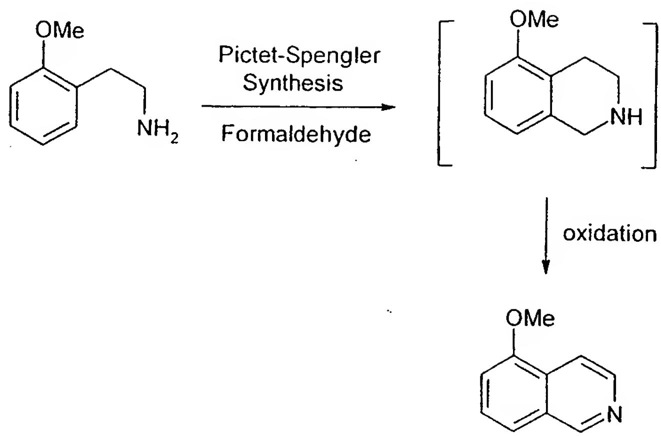


i. Illustrative Preparation of a 3-Indolylboronic Acid

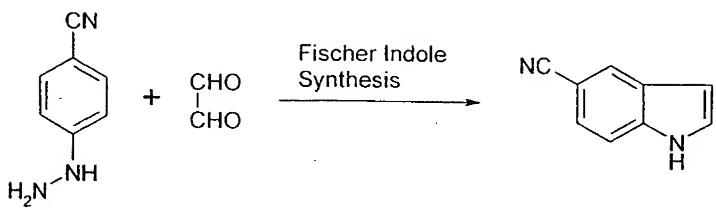


Isoquinoline, and congeneric, substrates that will ultimately be incorporated into subject antibacterials can be purchased or prepared from readily available starting materials utilizing well-known chemical transformations. The following schemes are illustrative of this fact.

j. Illustrative Isoquinoline Synthesis



k. Illustrative Indole Synthesis



l. Combinatorial Libraries

The compounds of the present invention, particularly libraries of variants having various representative classes of substituents, are amenable to combinatorial chemistry and other parallel synthesis schemes (see, for example, PCT WO 94/08051). The result is that large libraries of related compounds, e.g. a variegated library of compounds represented by formula **1** above, can be screened rapidly in high throughput assays in order to identify potential antibacterial lead compounds, as well as to refine the specificity, toxicity, and/or cytotoxic-kinetic profile of a lead compound. For instance, simple turbidimetric assays (e.g. measuring the A_{600} of a culture), or

spotting compounds on bacterial lawns, can be used to screen a library of the subject compounds for those having inhibitory activity toward a particular bacterial strain.

Simply for illustration, a combinatorial library for the purposes of the present invention is a mixture of chemically related compounds which may be screened together for a desired property. The preparation of many related compounds in a single reaction greatly reduces and simplifies the number of screening processes which need to be carried out. Screening for the appropriate physical properties can be done by conventional methods.

Diversity in the library can be created at a variety of different levels. For instance, the substrate aryl groups used in the combinatorial reactions can be diverse in terms of the core aryl moiety, e.g., a variegation in terms of the ring structure, and/or can be varied with respect to the other substituents.

A variety of techniques are available in the art for generating combinatorial libraries of small organic molecules such as the subject antibacterials. See, for example, Blondelle et al. (1995) Trends Anal. Chem. 14:83; the Affymax U.S. Patents 5,359,115 and 5,362,899: the Ellman U.S. Patent 5,288,514: the Still et al. PCT publication WO 94/08051; Chen et al. (1994) JACS 116:2661: Kerr et al. (1993) JACS 115:252; PCT publications WO92/10092, WO93/09668 and WO91/07087; and the Lerner et al. PCT publication WO93/20242). Accordingly, a variety of libraries on the order of about 100 to 1,000,000 or more diversomers of the subject antibacterials can be synthesized and screened for particular activity or property.

In an exemplary embodiment, a library of candidate antibacterial diversomers can be synthesized utilizing a scheme adapted to the techniques described in the Still et al. PCT publication WO 94/08051, e.g., being linked to a polymer bead by a hydrolyzable or photolyzable group e.g., located at one of the positions of the candidate antibacterials or a substituent of a synthetic intermediate. According to the Still et al. technique, the library is synthesized on a set of beads, each bead including a set of tags identifying the particular diversomer on that bead. The bead library can then be "plated" on a lawn of bacteria for which an inhibitor is sought. The diversomers can be released from the bead, e.g. by hydrolysis. Beads surrounded by areas of no, or diminished, bacterial growth, e.g. a "halo", can be selected, and their tags can be "read" to establish the identity of the particular diversomer.

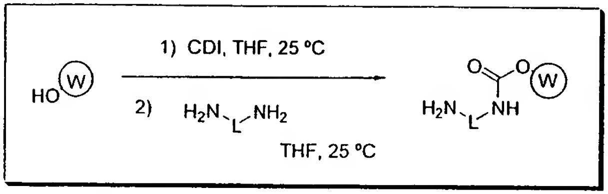
Exemplification

The invention now being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of

certain aspects and embodiments of the present invention, and are not intended to limit the invention.

Example 1

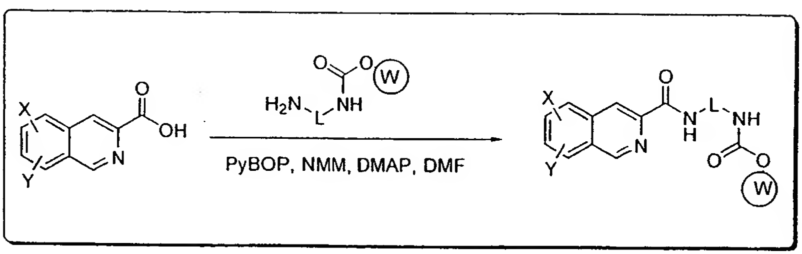
Synthesis of a Resin-Bound Diamine



To a 200 mL glass frit flask was added 10 g (8.0 mmol) of Wang resin, 13.0 g (80 mmol) of CDI, and 100 mL of THF. The reaction mixture was agitated on an orbital shaker for 24 h. The reaction mixture was filtered and the resin washed with THF (3x100 mL). To the glass frit flask containing the activated resin was added diamine (80 mmol) dissolved in 100 mL of THF. The reaction mixture was agitated on an orbital shaker for 24 h. The reaction mixture was filtered and the resin washed with THF (3x100 mL), DMF (3x100 mL), MeOH (3x100 mL), and DCM (3x100 mL) and dried under vacuum to give 11.3 g (0.70 mmol/g) of resin.

Example 2

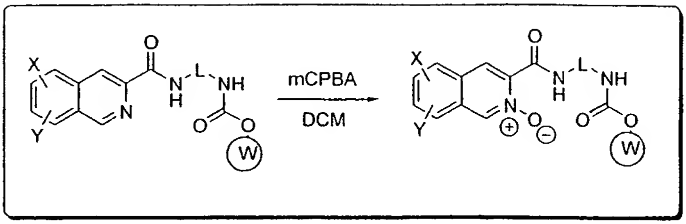
Synthesis of a Resin-Bound Isoquinoline-3-aminoalkylcarboxamide



To a 10 mL pear bottom flask was added of 3-isoquinolinecarboxylic acid (0.088 mmol), 46 mg (0.088 mmol) of PyBOP, 1 mL of DMF and 19 uL (0.176 mmol) of *N*-methylmorpholine. The reaction mixture was stirred for 10 min and then added to a 3 mL plastic tube fitted with a frit containing 50 mg of diamine-capped resin (0.035 mmol) and ~1 mg (0.001 mmol) of DMAP. The reaction mixture was agitated overnight on an orbital shaker at ambient temperature. The solvent was removed by filtration and the resin washed successively with DMF (3x3 mL), MeOH (3x3 mL), and DCM (3x3 mL) and dried under vacuum to give resin-bound isoquinoline-3-aminoalkylcarboxamide.

Example 3

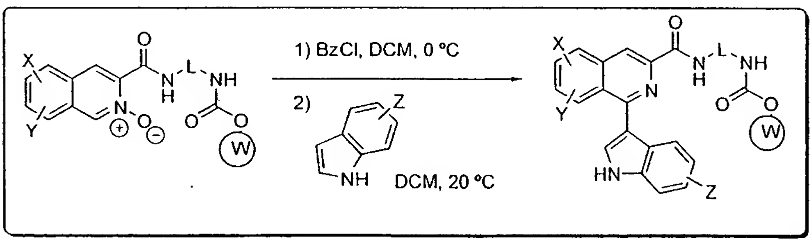
Synthesis of a Resin-Bound Isoquinoline-3-aminoalkylcarboxamide-*N*-oxide



To 50 mg of resin-bound isoquinoline-3-aminoalkylcarboxamide (0.035 mmol) in 2 mL of DCM in a 3 mL plastic tube fitted with a frit was added 60 mg (0.35 mmol) of *m*-CPBA. The reaction mixture was agitated at ambient temperature on an orbital shaker for 24 h. The solvent was removed by filtration and the resin washed successively with DMF (3x3 mL), MeOH (3x3 mL), and DCM (3x3 mL) and dried under vacuum to give resin-bound isoquinoline-3-aminoalkylcarboxamide-*N*-oxide.

Example 4

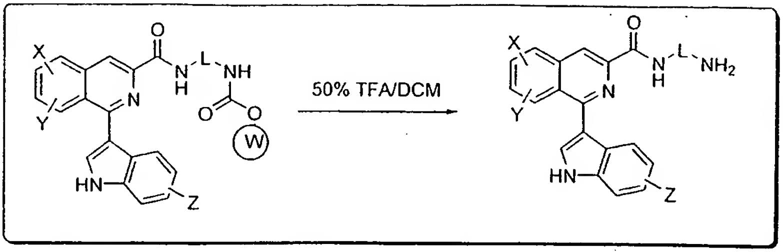
Synthesis of a Resin-Bound 1-(3-Indolyl)isoquinoline-3-aminoalkylcarboxamide



To a 3 mL plastic tube fitted with a frit containing 50 mg of resin-bound isoquinoline-3-aminoalkylcarboxamide-*N*-oxide at 0 °C was added 12 uL (0.11 mmol) of benzoyl chloride. The reaction mixture was agitated on an orbital shaker for 15 minutes and then indole (0.17 mmol) was added as a solid. The reaction mixture was agitated on an orbital shaker at ambient temperaure for 24 h. The solvent was removed by filtration and the resin washed successively with DMF (3x3 mL), MeOH (3x3 mL), and DCM (3x3 mL) and dried under vacuum to give resin-bound 1-(3-indolyl)isoquinoline-3-aminoalkylcarboxamide.

Example 5

Cleavage from the Resin Support of a 1-(3-Indolyl)isoquinoline-3-aminoalkylcarboxamide



To a 3 mL plastic tube fitted with a frit containing 50 mg of resin-bound 1-(3-indolyl)isoquinoline-3-aminoalkylcarboxamide (0.035 mmol) was added 1 mL of a 50% mixture of TFA and DCM. The reaction mixture was agitated on an orbital shaker for 30 min. The mixture was filtered and the resin washed with DCM (3x3 mL). The organic solutions were combined and evaporated by a stream of N_2. The residual solid was lyopholized to give 1-(3-indolyl)isoquinoline-3-aminoalkylcarboxamide (80-100% yield).

Example 6

Procedure for the Determination of MIC Values

Stock solutions of compounds are prepared with a concentration of 10 mg/mL. These solutions are then diluted 1:4 to give a concentration of 2.5 mg/mL. The compounds are then serially diluted 1:2 for 6 iterations. The concentrations made for each compound are 2.5, 1.25, 0.625, 0.3125, 0.156, 0.078, and 0.039 mg/mL. A control sample (no compound) is run along with each compound tested. All dilutions are made in DMSO.

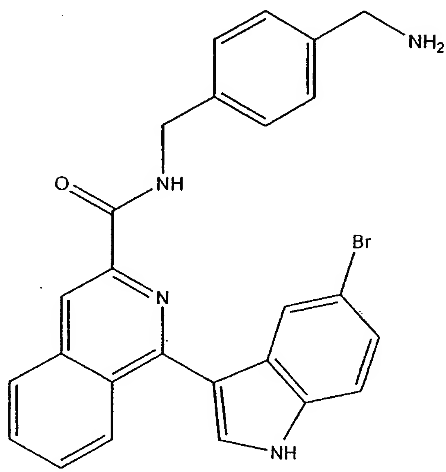
All wells of a 96 well microtiter plate are filled with 100 µL of BHI (Brain-Heart Infusion) broth. Columns on the plate are labeled 1-12, and rows are labeled A-H. Each column of wells is used to test one series of diluted compounds. Into each well of 100 µL of BHI broth, 1 µL of diluted compound is placed for a 1:100 dilution. This makes the final concentration of each drug series 25, 12.5, 6.25, 3.125, 1.56, 0.78, 0.39, and 0 µg/mL.

Test Organism: A sterile 15 mL screw cap tube is filled wth 3 mL of BHI broth. Next, 2-3 colonies of test organism are inoculated into the tube. The tube is then incubated at 37 °C in a CO_2 (approx. 7%) atmosphere jar. The organisms are allowed to grow to the density of a 0.5 McFarland standard (10^8 cells/mL). The organism is then inoculated into each well of the microtiter plate containing the diluted compounds to be tested for MIC. The inoculum is 1 µL in volume and represents 10^5 to 10^6 cells/mL.

After inoculation the plates are covered and incubated at 37 °C and approx. 7-10% CO_2 atmosphere overnight (about 16 hours). The plates are then observed for growth, the well with the lowest concentration of drug and no observable growth represents the well determining the MIC.

Example 7

MIC Value for a 1-(3-Indolyl)isoquinoline



Bacterium	MIC (µg/mL)
MRSA	< 7
VREF	< 25

Example 8

Table of MIC Values (µg/mL) for Quinoline-Indole Compounds

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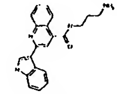
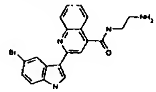
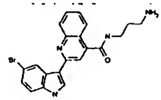
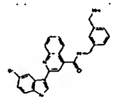
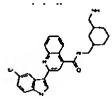
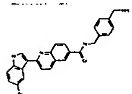
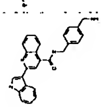
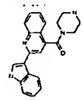
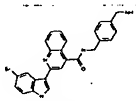
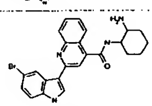
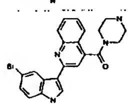
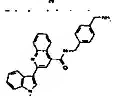
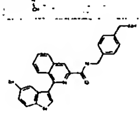
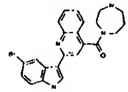
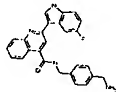
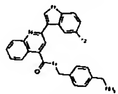
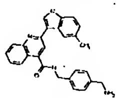
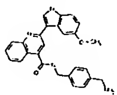
1		> 25	> 25	
2		< 25	< 25	
3		< 25	< 25	
4		< 25	< 7	
5		< 7	< 7	
6		> 25	> 25	
7		> 25	> 25	
8		> 25	> 25	
9		< 7	< 7	< 7
10		< 25	< 25	
11		< 25	< 25	
12		> 25	> 25	
13		< 7	< 25	

14		< 25	< 25
15		< 25	> 25
16		< 7	< 25
17		< 25	> 25
18		> 25	> 25
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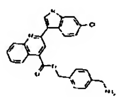
20		< 25	< 25
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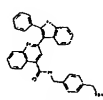
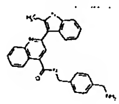
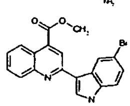
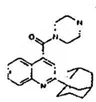
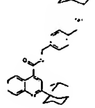
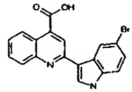
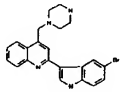
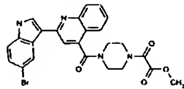
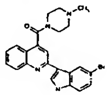
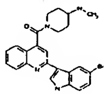
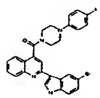
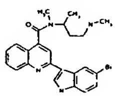
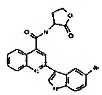
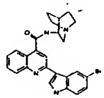
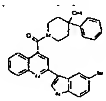
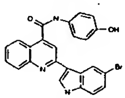
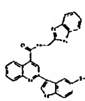
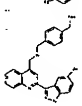
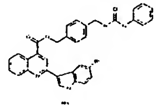
22		> 25	> 25
23		> 25	> 25
24		> 25	> 25
25		> 25	> 25
26		< 25	< 25

27		>	25	>	25
28		<	25	<	25
29		<	25	<	25
30		<	25	>	25
31		<	25	<	25
32		<	25	<	25
33		<	7	<	7
34		<	25	<	25
35		<	25	>	25
36		<	25	<	25
37		<	7	>	25
38		<	7	>	25
39		<	7	<	7

40		>	25	>	25		
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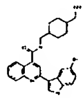
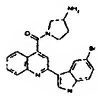
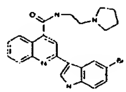
42		>	25	<	25		
43		<	25	<	25		
44		<	25	<	25		
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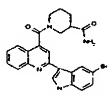
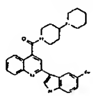
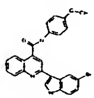
46		<	25	<	25		
47		<	25	<	25		
48		<	7	>	25	<	7
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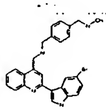
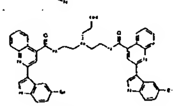
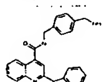
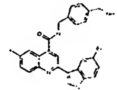
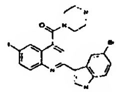
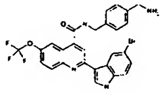
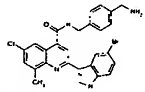
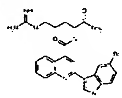
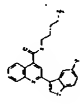
50		<	7	<	25		
51		<	7	<	7		
52		<	25	<	25		

53		<	7	<	7	<	7
54		<	7	<	7		
55		<	7	<	7		
56		<	25	<	25		
57		<	25	<	25		
58		<	25	<	25		
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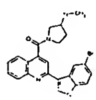
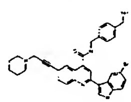
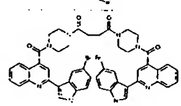
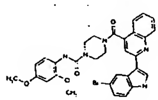
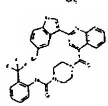
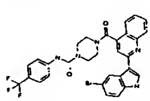
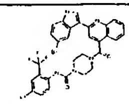
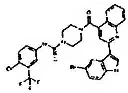
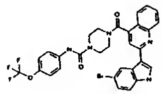
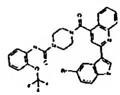
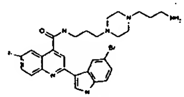
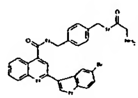
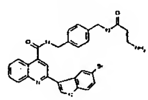
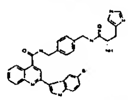
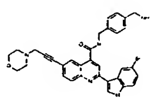
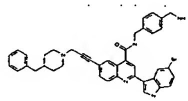
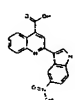
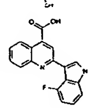
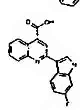
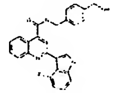
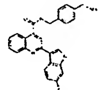
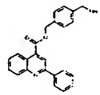
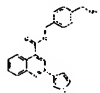
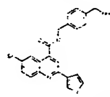
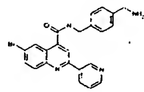
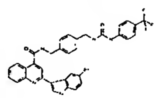
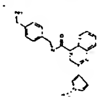
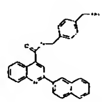
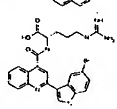
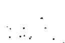
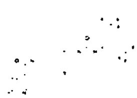
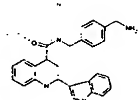
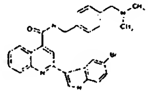
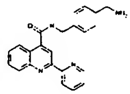
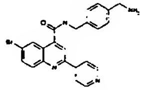
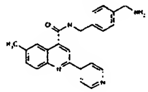
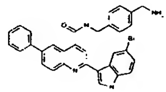
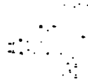
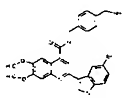
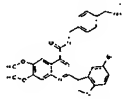
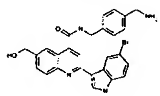
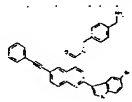
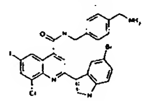
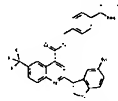
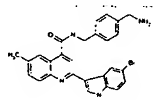
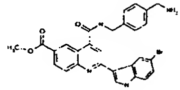
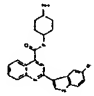
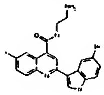
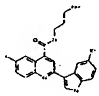
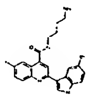
60		<	25	<	25		
61		<	7	<	7	<	7
62		>	25	>	25		
63		>	25	>	25		
64		>	25	>	25		
65		<	25	<	7		

66		>	25	>	25		
67		<	7	<	7		
68		<	7	<	7		
69		>	25	>	25		
70		<	7	<	25		
71		<	25	>	25		
72		>	25	>	25		
73		<	25	<	25		
74		<	7	<	25		
75		>	25	>	25		
76		>	25	>	25	>	25
77		>	25	>	25		
78		>	25	>	25		

79		>	25	>	25
80		<	25	<	25
81		>	25	>	25
82		>	25	>	25
83		>	25	>	25
84		<	7	<	25
85		<	7	<	25
86		>	25	>	25
87		<	25	<	25
88		>	25	>	25
89		<	25	>	25
90		<	25	<	7
91		>	25	>	25

92		<	25	<	25		
93		>	25	>	25		
94		>	25	>	25		
95		>	25	>	25		
96		<	7	<	7	<	7
97		>	25	>	25		
98		<	25	<	25		
99		<	25	<	25		
100		>	25	>	25		
101		<	7	<	7		
102		<	7	<	7	<	7
103		<	7	<	7	<	7
104		<	7	<	7	<	7

105		>	25	<	25		
106		<	25	<	25		
107		<	7	<	7	<	7
108		<	7	<	7	<	7
109		<	7	<	7	<	7
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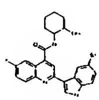
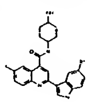
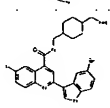
112		<	7	<	7	<	7
113		<	7	<	7	<	7
114		<	7	<	7	<	7
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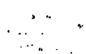
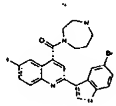
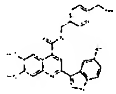
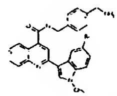
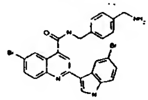
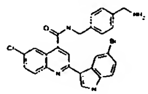
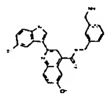
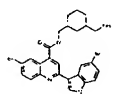
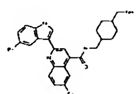
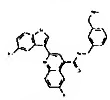
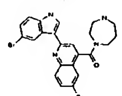
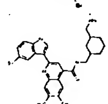
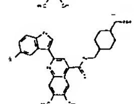
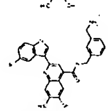
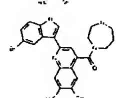
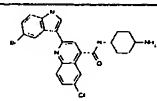
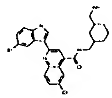
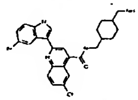
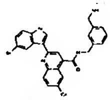
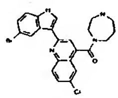
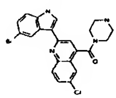
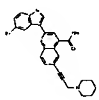
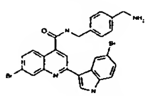
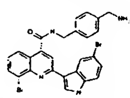
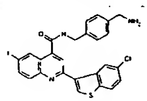
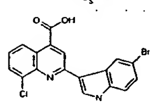
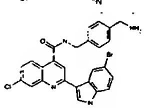
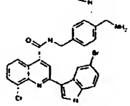
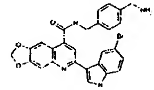
116		<	7	<	7	<	7
117		<	7	<	7	<	7

118		< 7	< 7	< 7
119		< 7	< 25	< 7
120		< 7	< 7	
121		< 7	< 7	
122		< 7	< 7	< 7
123		< 7	< 7	< 7
124		< 7	< 7	< 7
125		< 7	< 7	
126		< 7	< 7	
127		< 7	< 7	< 7
128		< 7	< 7	< 7
129		< 7	< 7	
130		< 7	< 7	

131		<	7	<	25	<	7
132		<	7	<	7	<	7
133		<	7	<	7	<	7
134		<	7	<	7	<	7
135		<	7	<	7		
136		<	7	<	7	<	7
137		<	25	<	25		
138		<	7	<	7	<	7
139		<	7	<	7	<	7
140		>	25	<	25		
141		>	25	>	25		
142		<	7	<	7	<	7
143		<	7	<	7	<	7

144		<	7	<	25	<	25
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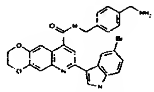
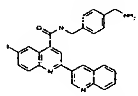
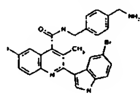
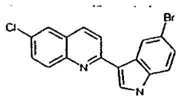
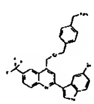
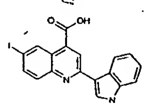
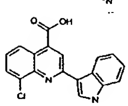
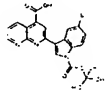
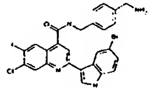
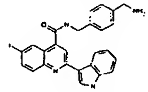
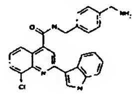
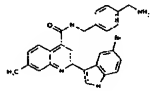
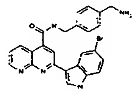
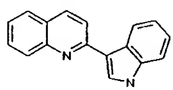
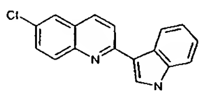
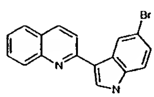
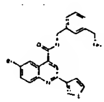
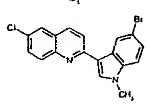
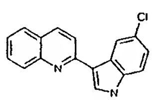
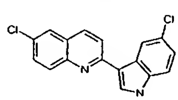
150		>	25	>	25		
151		>	25	>	25	>	25
152		<	7	<	25		
153		<	7	>	25	<	7
154		<	7	<	7	<	7
155		>	25	>	25		
156		>	25	>	25		

157		> 25	> 25	
158		< 7	< 7	< 7
159		< 7	< 25	< 25
160		< 25	< 25	
161		< 7	< 7	< 7
162		> 25	> 25	
163		< 25	> 25	> 25
164		< 7	< 5	< 7
165		< 7	< 7	< 7
166		> 25	> 25	
167		> 25	> 25	
168		< 7	> 25	< 7
169		< 7	> 25	< 7

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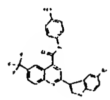
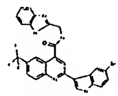
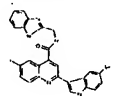
171		<	7	<	7	<	7
172		<	7	>	25	<	7
173		<	7	>	25	<	7
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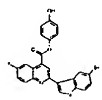
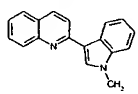
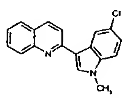
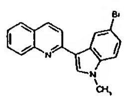
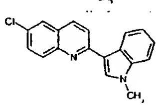
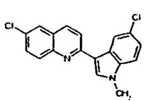
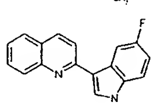
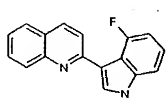
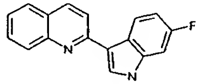
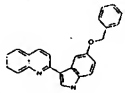
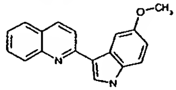
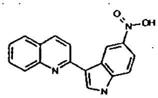
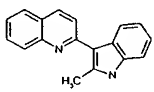
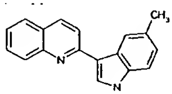
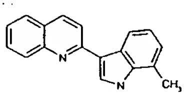
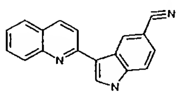
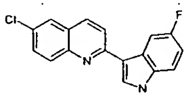
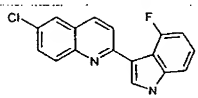
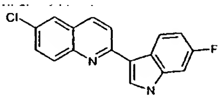
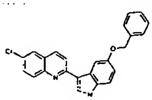
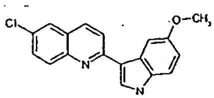
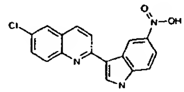
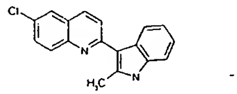
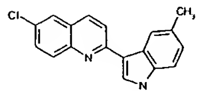
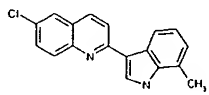
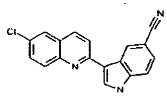
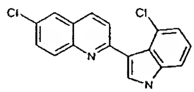
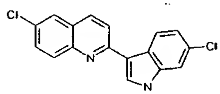
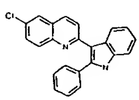
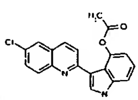
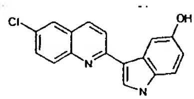
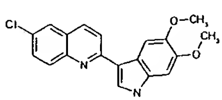
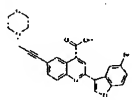
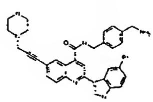
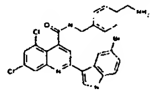
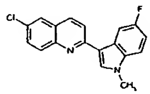
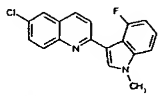
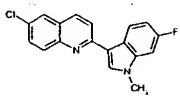
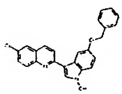
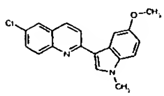
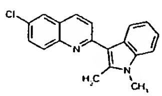
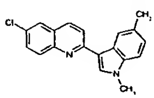
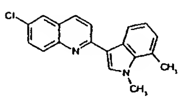
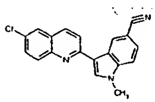
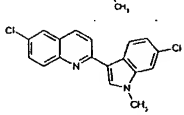
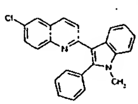
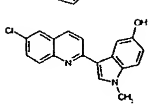
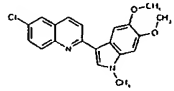
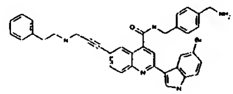
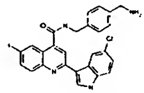
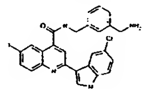
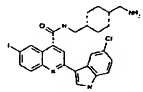
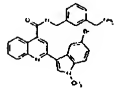
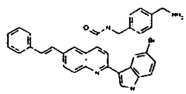
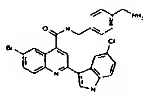
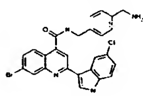
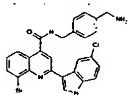
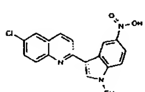
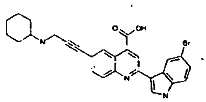
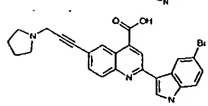
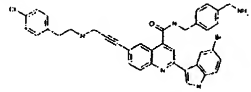
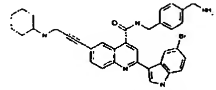
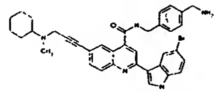
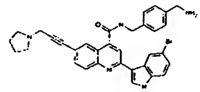
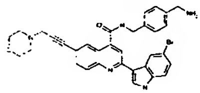
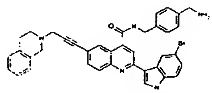
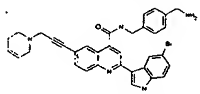
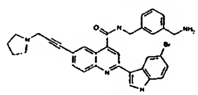
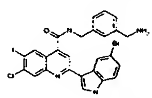
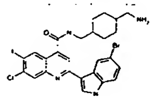
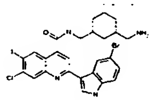
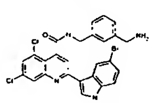
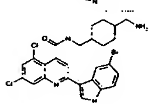
175		<	7	<	25	<	7
176		>	25	>	25		
177		>	25	>	25		
178		>	25	>	25		
179		>	25	>	25		
180		>	25	>	25		
181		<	7	<	25	<	7
182		>	25	>	25		

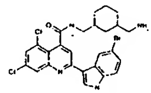
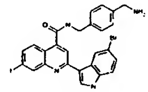
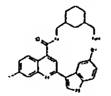
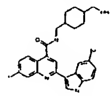
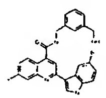
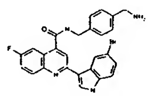
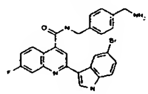
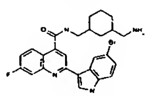
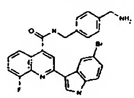
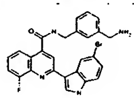
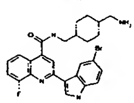
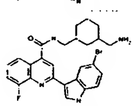
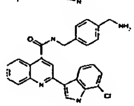
183		<	25	>	25	>	25
184		>	25	>	25	<	7
185		<	25	>	25		
186		>	25	>	25		
187		>	25	>	25		
188		>	25	>	25		
189		<	25	<	25		
190		>	25	>	25		
191		<	7	<	25	<	7
192		>	25	>	25		
193		<	7	<	7	<	7
194		<	7	>	25	<	7
195		>	25	>	25	>	25

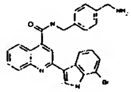
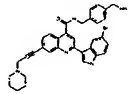
196		<	7	>	25	<	25
197		<	7	>	25		
198		>	25	>	25		
199		>	25	>	25	>	25
200		<	7	>	25	>	25
201		<	7	<	25	<	7
202		<	7	>	25	<	7
203		>	25	>	25		
204		<	7	<	25	<	7
205		<	25	<	25		
206		>	25	>	25		
207		>	25	<	25		
208		<	7	<	25	<	25

209		<	7	<	7	<	7
210		<	7	>	25		
211		<	25	>	25	>	25
212		>	25	>	25		
213		<	25	<	25		
214		<	25	>	25		
215		<	7	<	25		
216		<	25	>	25		
217		<	25	<	25	<	7
218		<	7	>	25	>	25
219		>	25	>	25	<	25
220		<	25	>	25		
221		<	7	<	7	<	7

222		> 25	> 25	
223		< 7	< 7	< 7
224		< 7	< 7	< 7
225		< 7	< 7	< 7
226		< 25	< 25	< 7
227		< 7	< 7	< 7
228		> 25	> 25	> 25
229		< 7	< 7	< 7
230		< 7	< 7	< 7
231		< 7	< 7	< 7
232		< 7	< 7	< 7
233		> 25	< 25	< 25
234		> 25	> 25	> 25

235		< 7	< 7	< 7
236		< 7	< 7	< 7
237		< 7	< 7	
238		< 7	< 25	< 7
239		< 7	< 7	> 25
240		< 7	< 25	> 25
241		< 7	< 7	< 7
242		< 7	< 25	< 7
243		< 7	< 7	< 7
244		< 7	< 7	< 7
245		< 7	< 7	< 7
246		< 7	< 7	< 7
247		< 7	< 7	< 7

248		<	7	<	7	<	7
249		<	7	<	7	<	7
250		<	7	<	7	<	7
251		<	7	<	7	<	7
252		<	7	<	7	<	7
253		<	7	<	25	<	7
254		<	7	<	7	<	7
255		<	7	<	7		
256		<	7	<	7	<	7
257		<	7	<	7	<	7
258		<	7	<	7	<	7
259		<	7	<	7	<	7
260		<	25	<	25	<	25

261		< 25	< 25	< 25
262		< 7	< 7	< 7
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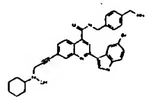
264		< 7	< 25	
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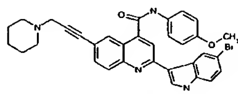
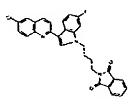
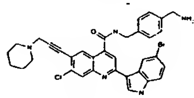
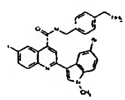
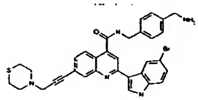
266		< 7	> 25	< 7
267		> 25	> 25	
268		< 7	< 7	
269		< 7	< 7	
270		< 25	< 25	> 25
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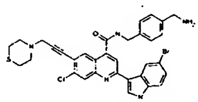
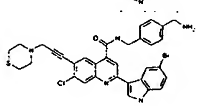
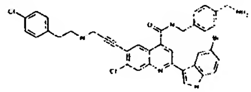
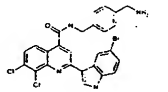
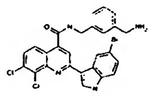
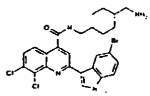
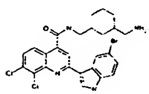
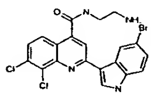
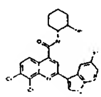
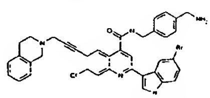
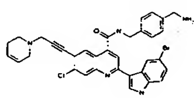
272		< 7	< 7	< 7
273		< 7	< 7	< 7

274		<	25	>	25	<	7
275		<	7	<	7	<	25
276		<	7	<	7	>	25
277		<	7	<	7	<	7
278		<	7	<	7	<	7
279		<	7	<	7	<	7
280		<	7	<	7	<	7
281		<	25	>	25	>	25
282		<	7	<	7	<	7

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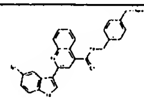
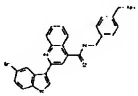
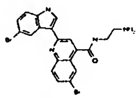
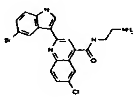
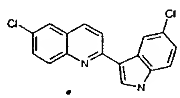
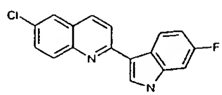
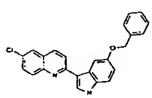
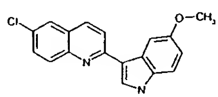
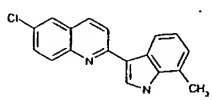
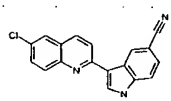
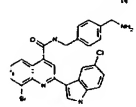
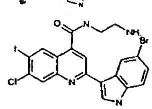
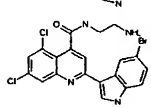
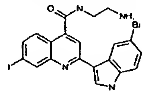
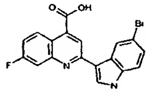
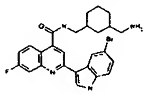
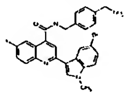
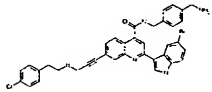
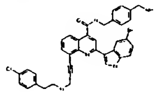
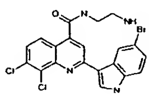
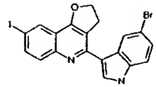
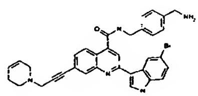
283		< 7	< 7	< 7
284		< 7 [CRSA]	< 7	< 7
285		< 7	< 7	< 7
286		< 7 [CRSA]	< 7	< 7
287		< 7	> 25	< 7
288		< 7	< 7	< 7
289		< 7	> 25	< 7
290		> 25	> 25	> 25
291		> 25	> 25	> 25
292		> 25	> 25	> 25
293		< 7	< 7	< 7
294		< 7	< 7	< 7
295		< 7	< 7	< 7

296		<	7 [CRSA]	<	7	<	7
297		<	25	<	25	<	25
298		<	7	<	7	<	7
299		<	7	<	7	<	7
300		<	7	<	7	<	25
301		<	7	<	25	<	25
302		<	7	<	7	<	7
303		<	7	>	25	<	7
304		<	7	<	7	<	7
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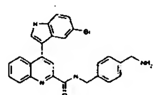
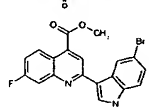
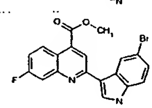
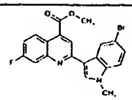
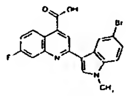
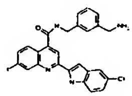
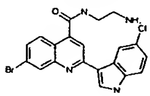
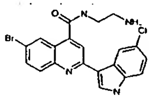
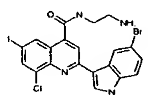
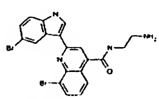
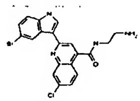
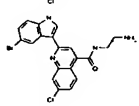
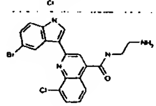
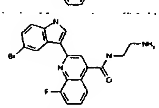
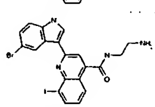
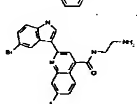
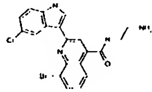
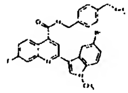
306		<	7	<	7	<	7
307		<	7	<	7	<	7
308		<	7	<	7	<	7

309		>	25	>	25	>	25
310		<	25	>	25	<	25
311		>	25	>	25	>	25
312		<	7	<	7	<	7
313		<	7	<	7	<	7
314		<	7	<	7	<	7
315		<	7	<	7	<	7
316		<	7	<	7	<	7
317		<	7	<	7	<	7
318		<	7	<	7	<	7
319		<	7	<	25	<	7
320		<	7 [CRSA]	<	7	<	7
321		<	7	<	7	<	7

322		<	7	<	7	<	7
323		<	7 [CRSA]	<	25	<	7
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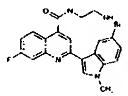
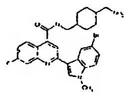
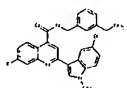
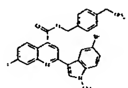
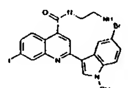
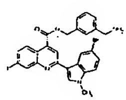
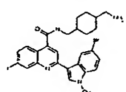
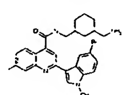
325		<	7	<	7	<	7
326		<	7	<	7	<	7
327		<	25	>	25	<	7
328		>	25	>	25	<	7
329		<	7 [CRSA]	<	7	<	7
330		<	7	<	7	<	7
331		<	7	<	7	<	7
332		<	7	<	7	<	7
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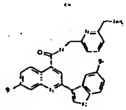
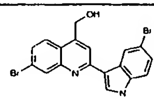
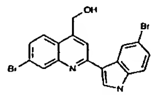
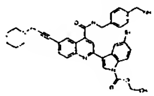
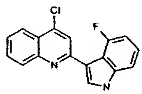
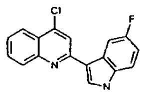
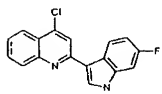
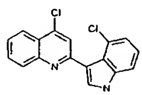
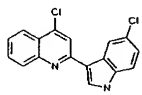
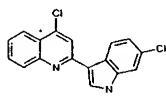
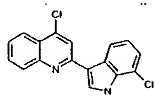
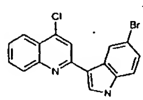
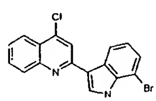
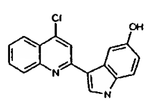
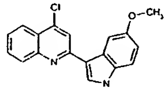
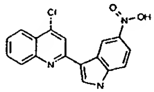
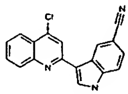
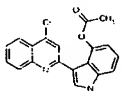
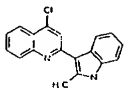
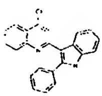
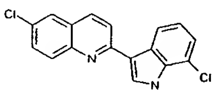
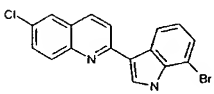
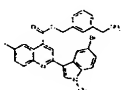
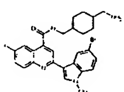
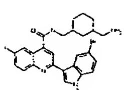
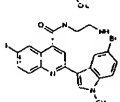
334		<	7	<	7	<	7

335		<	7	<	7	<	7
336		<	7	<	7	<	7
337		>	25	>	25	>	25
338		<	25	>	25	<	7
339		<	7	<	7	<	7
340		<	7	<	7	<	7
341		<	7	<	7	<	7
342		<	7	>	25	<	7
343		<	7	>	25	<	7
344		<	7	>	25	<	7
345		<	7	>	25	<	7
346		<	25	>	25	<	25
347		<	25	>	25	<	25

348		<	7	>	25	<	7
349		>	25	>	25	>	25
350		>	25	>	25	>	25
351		<	7	>	25	<	7
352		<	7	>	25	<	7
353		>	25	>	25	>	25
354		>	25	>	25	>	25
355		>	25	>	25	>	25
356		<	7	<	7	<	7
357		<	7	<	7	<	7
358		<	7	<	7	<	7
359		<	7	<	7	<	7
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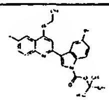
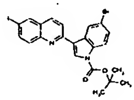
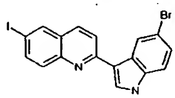
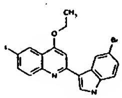
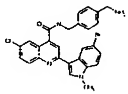
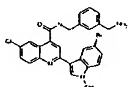
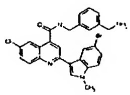
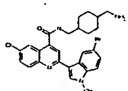
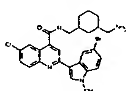
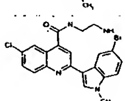
361		>	25	>	25	>	25
362		>	25	>	25	>	25
363		<	7	<	7	<	7
364		<	7	<	25	<	7
365		<	7	<	7	<	7
366		>	25	>	25	>	25
367		>	25	>	25	>	25
368		<	7	<	7	<	7
369		<	7	<	7	<	7
370		<	7	<	7	<	7
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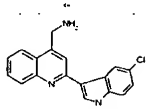
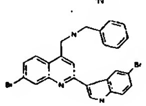
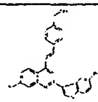
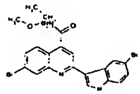
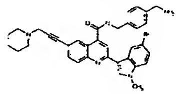
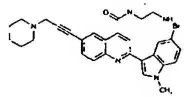
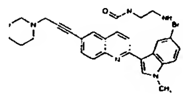
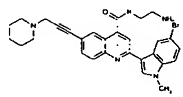
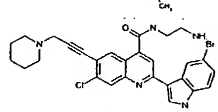
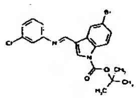
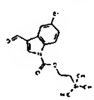
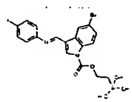
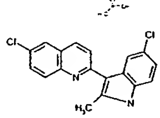
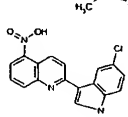
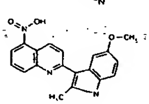
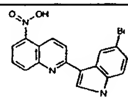
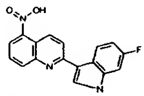
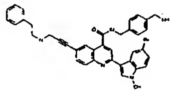
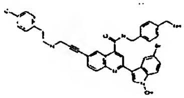
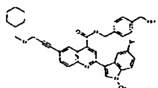
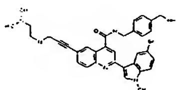
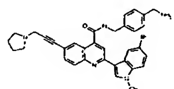
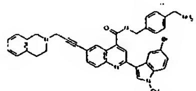
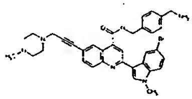
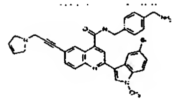
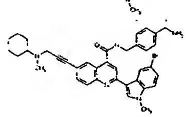
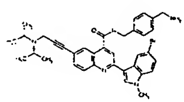
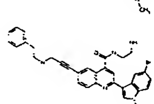
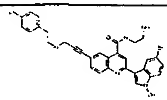
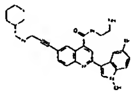
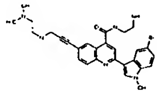
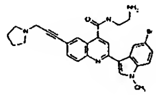
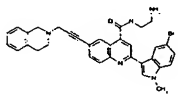
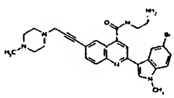
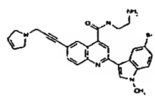
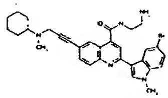
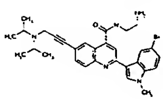
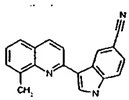
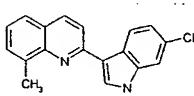
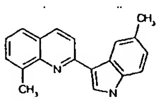
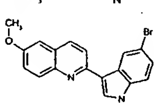
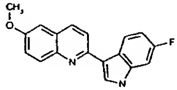
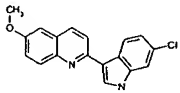
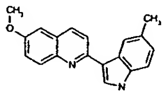
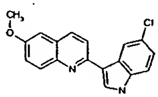
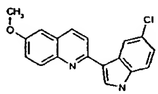
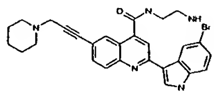
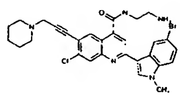
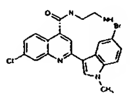
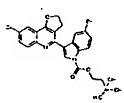
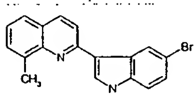
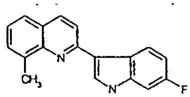
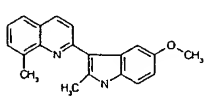
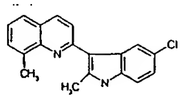
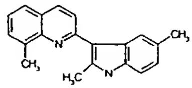
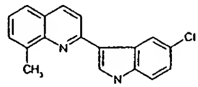
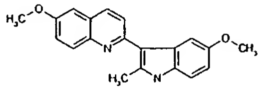
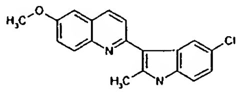
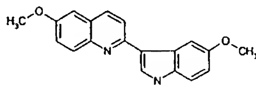
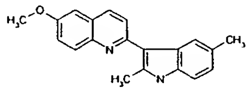
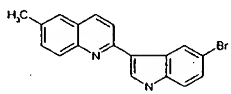
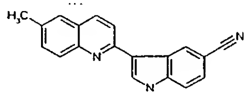
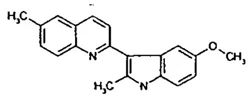
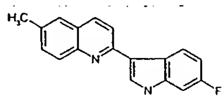
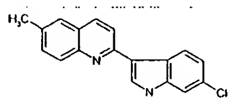
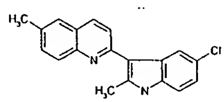
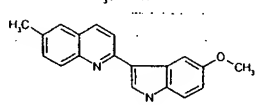
372		<	7	<	25	<	7
373		<	7	<	7	<	7

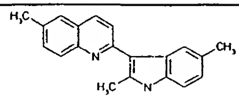
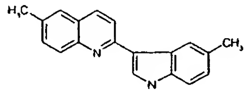
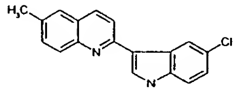
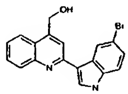
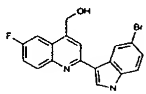
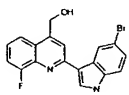
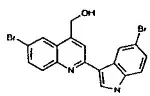
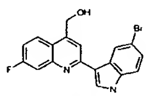
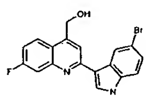
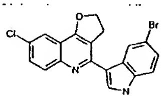
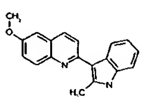
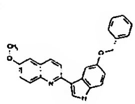
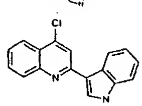
374		<	7	<	7	<	7
375		>	25	>	25	>	25
376		<	25	<	25	<	7
377		<	7	<	7	<	7
378		<	7	<	7	<	7
379		<	7	<	7	<	7
380		<	7	<	7	<	7
381		>	25	>	25	>	25
382		>	25	>	25	>	25
383		>	25	>	25	>	25
384		<	7	>	25	<	7
385		>	25	>	25	>	25
386		>	25	>	25	>	25

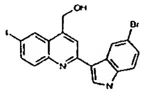
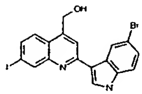
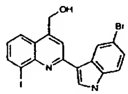
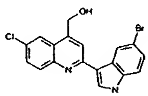
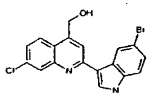
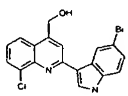
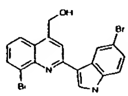
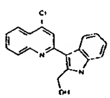
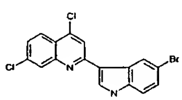
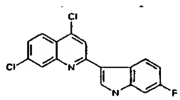
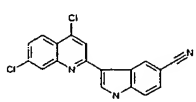
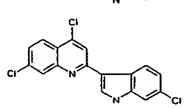
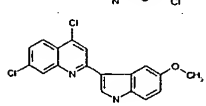
387		>	25	>	25	>	25
388		>	25	>	25	>	25
389		<	7	<	7	<	25
390		<	25	<	7	<	7
391		<	7	<	7	<	7
392		<	7	<	7	<	7
393		<	7	<	25	<	25
394		>	25	>	25	>	25
395		<	7	<	25	<	25
396		>	25	>	25	>	25
397		<	7	<	7	<	7
398		<	7	<	7	<	7
399		<	7	<	7	<	7

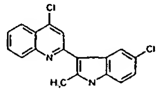
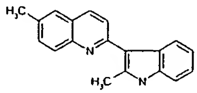
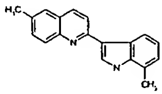
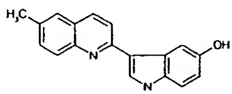
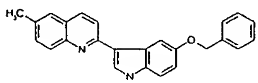
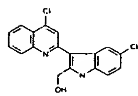
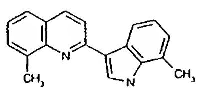
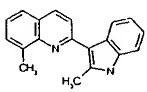
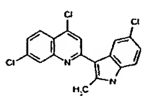
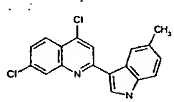
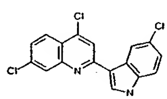
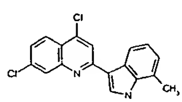
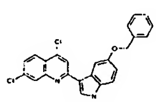
400		<	7	<	7	<	7
401		<	7	<	7	<	7
402		<	7	<	7	<	7
403		<	7	<	7	<	7
404		<	7	<	7	<	7
405		<	25	<	25	<	25
406		<	7	<	7	<	7
407		<	7	<	7	<	7
408		<	7	<	7	<	7
409		>	25	>	25	>	25
410		<	25	>	25	<	25
411		>	25	>	25	>	25
412		<	7	>	25	>	25

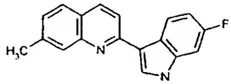
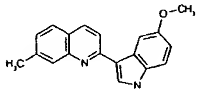
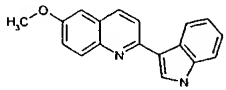
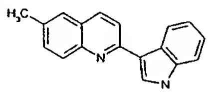
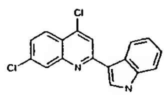
413		>	25	>	25	>	25
414		>	25	>	25	>	25
415		<	7	>	25	>	25
416		<	7	>	25	<	7
417		<	7	>	25	<	7
418		<	7	<	7	<	7
419		<	7	<	7	<	7
420		<	7	<	7	<	7
421		>	25	>	25	>	25
422		>	25	>	25	>	25
423		>	25	>	25	>	25
424		<	25	>	25	<	25
425		<	7	<	7	<	7

426		<	25	>	25	<	25
427		>	25	>	25	>	25
428		>	25	>	25	>	25
429		<	7	>	25	<	7
430		<	25	>	25	<	25
431		>	25	>	25	>	25
432		<	7	>	25	<	7
433		<	7	>	25	<	&
434		>	25	>	25	>	25
435		>	25	>	25	>	25
436		<	7	>	25	<	7
437		<	7	>	25	<	7
438		>	25	>	25	>	25

439		>	25	>	25	>	25
440		>	25	>	25	<	25
441		>	25	>	25	>	25
442		<	7	<	25	<	7
443		<	7	<	25	<	7
444		<	7	<	25	<	7
445		<	7	<	7	<	7
446		<	7	<	7	<	7
447		<	7	<	7	<	7
448		<	7	>	25	<	25
449		>	25	>	25	>	25
450		>	25	>	25	>	25
451		<	7	>	25	<	7

452		<	7	>	25	<	7
453		<	7	<	7	<	7
454		<	7	<	7	<	7
455		<	7	<	7	<	7
456		<	7	<	7	<	7
457		<	7	<	7	<	7
458		<	7	<	7	<	7
459		>	25	>	25	>	25
460		<	7	<	7	<	7
461		<	7	<	7	<	7
462		>	25	>	25	>	25
463		=	25	>	25	=	25
464		<	7	>	25	<	7

465		<	7	<	25	<	7
466		>	25	>	25	<	25
467		>	25	>	25	>	25
468		=	25	>	25	>	25
469		<	7	>	25	<	7
470		>	25	>	25	>	25
471				>	25	<	7
472		<	25	>	25	<	25
473		<	7	<	25	<	7
474		<	7	<	25	<	7
475		<	7	<	7	<	7
476		>	25	>	25	<	25
477		<	7	>	25	<	7

478		>	25	>	25	>	25
479		>	25	>	25	<	25
480		>	25	>	25	>	25
481		>	25	>	25	>	25
482		<	7	<	7	<	7

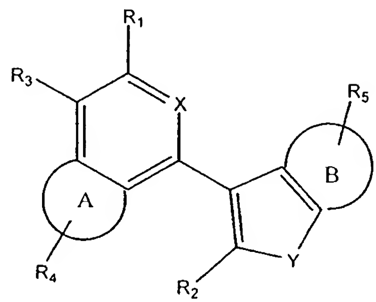
All of the references cited in this document are hereby incorporated by reference.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

We claim:

1. A compound represented by the general formula 1:



1

wherein

each of A and B independently represent fused rings selected from a group consisting of monocyclic or polycyclic cycloalkyls, cycloalkenyls, aryls, and heterocyclic rings, said rings comprising from 4 to 8 atoms in a ring structure;

X represents CR, N, N(O), P, or As;

Y represents CR_2, NR, O, PR, S, AsR, or Se;

R, R_1, R_2, and R_3, for each occurrence, independently represent hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

R_4 and R_5, for each occurrence, independently represent halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

A and B independently may be unsubstituted or substituted with R_4 and R_5, respectively, any number of times up to the limitations imposed by stability and the rules of valence;

R_{80} represents an unsubstituted or substituted aryl, a cycloalkyl, a cycloalkenyl, a heterocycle , or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

2. The compound of claim 1, 4, 7, 18 or 21, wherein X represents N.

3. The compound of claim 1 or 2, wherein Y represents NR.

4. The compound of claim 1, wherein R_1 represents -C(Z)N(R)(R'-NHR).

5. The compound of claim 4 or 7, wherein R' represents an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, or heteroaryl.

6. The compound of claim 5, wherein R' represents a cycloalkyl.

7. The compound of claim 4, wherein

R_2 and R_3, independently for each occurrence, represent H or a hydrophobic aliphatic group;

R_4, independently for each occurrence, represents C_1-C_6 alkyl, 1-alkenyl, 1-alkynyl, aryl, -OR, $-OCF_3$, $-OC(R)_2OR$, $-C(R)_2OR$, $-CO_2R$, or a small hydrophobic moiety; and

R_5, independently for each occurrence, represents a small hydrophobic moiety.

8. The compound of claim 7, wherein R_2 and R_3 independently for each occurrence represent H, a C_1-C_6 alkyl or aryl.

9. The compound of claim 7, wherein A and B each represent fused benzo rings, X represents N, Y represents NR_a, and R_a represents H, alkyl, alkylsulfonyl, arylsulfonyl, or $-(CH_2)_m-R_{80}$, wherein R_{80} represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle, and m is an integer in the range 0 to 8 inclusive.

10. The compound of claim 7, 8 or 9, wherein R_4 occurs at least once and represents a halogen or a 1-alkynyl.

11. The compound of claim 10, wherein

R_4 occurs at least once and represents $-CCR_{60}$; and

R_{60} represents hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, aminoalkyl, alkylamino, sulfhydryl, alkylthio, imine, amide, carbonyl, carboxyl, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, heteroalkyl, nitrile, amidine, amine oxide, aryl, heteroaryl, carbamate, imide, oxime, sulfonamide, thioamide, urea, or $-(CH_2)_m-R_{80}$.

12. The compound of claim 7, 8 or 9, wherein R_5 occurs at least once and represents a halogen.

13. The compound of claim 11, wherein R_5 occurs at least once and represents a halogen.

14. The compound of claim 3, wherein Y represents NR_a, and R_a represents H, alkyl, alkylsulfonyl, arylsulfonyl, or $-(CH_2)_m-R_{80}$, wherein R_{80} represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle, and m is an integer in the range 0 to 8 inclusive.

15. The compound of claim 10, having a minimum inhibitory concentration (MIC) less than 10 μg/mL against at least one Gram-positive bacterium.

16. The compound of claim 7 or 8, having a minimum inhibitory concentration (MIC) less than 10 μg/mL against at least one Gram-positive bacterium.

17. The compound of claim 12, having a minimum inhibitory concentration (MIC) less than 10 μg/mL against at least one Gram-positive bacterium.

18. The compound of claim 1, wherein

R_1 represents halogen, $-C(Z)OR$, $-C(Z)N(R)_2$, $-S(Z)_2N(R)_2$, or $-P(Z)_2N(R)_2$;

Z independently for each occurrence represents $(R)_2$, O, S, or NR; and

R for each occurrence, independently represents hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$.

19. The compound of claim 18, wherein R_1 represents halogen, $-C(Z)OR$, or $-C(Z)N(R)_2$.

20. The compound of claim 18, wherein R_1 represents halogen, or $-C(Z)N(R)_2$.

21. The compound of claim 18, wherein

R_2 and R_3, independently for each occurrence, represent H or a hydrophobic aliphatic group; and

R_4, independently for each occurrence, represents C_1-C_6 alkyl, 1-alkenyl, 1-alkynyl, aryl, $-OR$, $-OCF_3$, $-OC(R)_2OR$, $-C(R)_2OR$, $-CO_2R$, or a small hydrophobic moiety.

22. The compound of claim 21, wherein R_2 and R_3 independently for each occurrence represent H, a C_1-C_6 alkyl or aryl.

23. The compound of claim 18, 19, 20, 21, 22 or 26, wherein R_4 occurs at least once and represents a halogen or a 1-alkynyl.

24. The compound of claim 23, wherein

R_4 occurs at least once and represents $-CCR_{60}$; and

R_{60} represents hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, aminoalkyl, alkylamino, sulfhydryl, alkylthio, imine, amide, carbonyl, carboxyl, silyl,

thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, heteroalkyl, nitrile, amidine, amine oxide, aryl, heteroaryl, carbamate, imide, oxime, sulfonamide, thioamide, urea, or $-(CH_2)_m-R_{80}$.

25. The compound of claim 24, wherein R_5 occurs at least once and represents a halogen.

26. The compound of claim 18, wherein Y represents NR_a, and R_a represents H, alkyl, alkylsulfonyl, arylsulfonyl, or $-(CH_2)_m-R_{80}$; wherein R_{80} represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle; and m is an integer in the range 0 to 8 inclusive.

27. The compound of claim 18, 21, 22 or 26, wherein R_5 independently for each occurrence represents a small hydrophobic moiety, $-C(O)N(R)_2$, -CN, $-NO_2$, -OH, -OR, $-O_2C$-aryl, or $-O_2C$-alkyl.

28. The compound of claim 27, wherein R_5 occurs at least once and represents a halogen, halogenated alkyl, $-C(O)N(R)_2$, -CN, $-NO_2$, -OH, -OR, $-O_2C$-aryl, or $-O_2C$-alkyl.

29. The compound of claim 27, having a minimum inhibitory concentration (MIC) less than 10 μg/mL against at least one Gram-positive bacterium.

30. The compound of claim 21 or 22, having a minimum inhibitory concentration (MIC) less than 10 μg/mL against at least one Gram-positive bacterium.

31. The compound of claim 23, having a minimum inhibitory concentration (MIC) less than 10 μg/mL against at least one Gram-positive bacterium.

32. The compound of claim 1, wherein R_1 represents a hydrogen.

33. The compound of claim 32, wherein

R_2 and R_3 independently for each occurrence represent H or a hydrophobic aliphatic group; and

R_4 independently for each occurrence represents C_1-C_6 alkyl, 1-alkenyl, 1-alkynyl, aryl, -OR, $-OCF_3$, $-OC(R)_2OR$, $-C(R)_2OR$, $-CO_2R$, or a small hydrophobic moiety.

34. The compound of claim 32, wherein R_2 and R_3 independently for each occurrence represent H, a C_1-C_6 alkyl, or aryl.

35. The compound of claim 33 or 24, wherein R_4 occurs at least once and represents a halogen or a 1-alkynyl.

36. The compound of claim 35, wherein

R_4 occurs at least once and represents $-CCR_{60}$; and

R_{60} represents hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, aminoalkyl, alkylamino, sulfhydryl, alkylthio, imine, amide, carbonyl, carboxyl, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, heteroalkyl, nitrile, amidine, amine oxide, aryl, heteroaryl, carbamate, imide, oxime, sulfonamide, thioamide, urea, or $-(CH_2)_m-R_{80}$.

37. The compound of claim 32 or 33, wherein R_5 independently for each occurrence represents a small hydrophobic moiety, $-C(O)N(R_a)_2$, -CN, $-NO_2$, -OH, $-OR_a$, $-O_2C$-aryl, or $-O_2C$-alkyl.

38. The compound of claim 37, wherein R_5 occurs at least once and represents a halogen, halogenated alkyl, $-C(O)N(R)_2$, -CN, $-NO_2$, -OH, -OR, $-O_2C$-aryl, or $-O_2C$-alkyl.

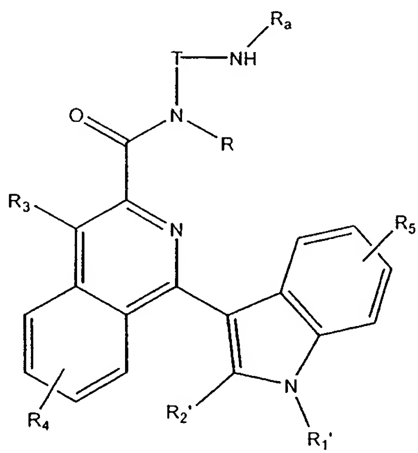
39. The compound of claim 1, wherein R_4 occurs at least once and represents at least one 1-alkynyl group.

40. The compound of claim 1, having a minimum inhibitory concentration (MIC) less than 10 μg/mL against at least one Gram-positive bacterium.

41. The compound of claim 40, wherein the bacterium is selected from the group consisting of *Staphylococcus spp* and *Enterococcus spp*.

42. The compound of claim 40, having a therapeutic index in primates of at least 10 for the inhibition of infection by at least one Gram-positive bacterium.

43. A compound represented by general formula 2:



2

wherein

R, R_a, R_3, R_1', and R_2', for each occurrence, independently represent hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine,

carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

R_4, and R_5, for each occurrence, independently represent halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

T represents a covalent linker;

the B-rings of the 1-isoquinolinyl and 3-indolyl moieties may be unsubstituted, or substituted between one and four times inclusive by R_4 and R_5, respectively;

R_{80} represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

44. The compound of claim 43, 46, 47, 48 or 49, wherein T represents a cyclic, branched or straight chain aliphatic group, 2-10 bonds in length.

45. The compound of claim 44, wherein T represents a cycloalkyl group.

46. The compound of claim 43, wherein

R_2' and R_3 independently for each occurrence represent H or a hydrophobic aliphatic group;

R_4 independently for each occurrence represents C_1-C_6 alkyl, 1-alkenyl, 1-alkynyl, aryl, -OR, $-OCF_3$, $-OC(R)_2OR$, $-C(R)_2OR$, $-CO_2R$, or a small hydrophobic moiety; and

R_5 independently for each occurrence represents a small hydrophobic moiety.

47. The compound of claim 36, wherein R_2' and R_3 independently for each occurrence represent H, C_1-C_6 alkyl or aryl.

48. The compound of claim 47, wherein R_2' and R_3 independently for each occurrence represent H or Me.

49. The compound of claim 48, wherein R, R_a and R'_1 independently for each occurrence represent H, alkyl, alkylsulfonyl, arylsulfonyl, or $-(CH_2)_m-R_{80}$; wherein R_{80} represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle; and m is an integer in the range 0 to 8 inclusive.

50. The compound of claim 43, 46, 47, 48 or 49, wherein R_4 occurs at least once and represents, independently for each occurence, halogen, a 1-alkynyl group or a trihalogenated methyl group.

51. The compound of claim 50, wherein R_4 occurs at least once and represents a 1-alkynyl group.

52. The compound of claim 50, wherein R_4 occurs at least once and represents a trihalogenated methyl group.

53. The compound of claim 50, wherein R_5 occurs at least once and represents a halogen.

54. The compound of claim 50, wherein R_5 occurs at least once and represents a halogenated C_1-C_6 alkyl group.

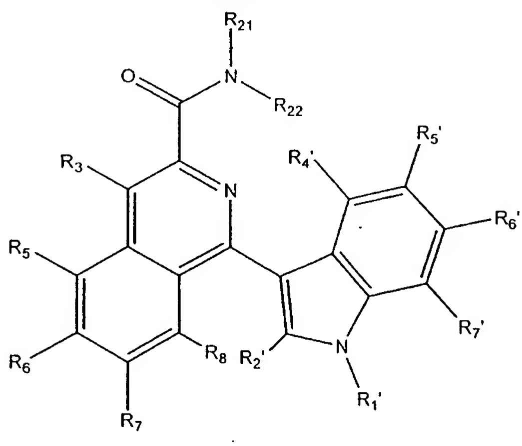
55. The compound of claim 43, 46, 47, 48 or 49, wherein R_5 occurs at least once and represents a halogen.

56. The compound of claim 43, 46, 47, 48 or 49, wherein R_5 occurs at least once and represents a halogenated C_1-C_6 alkyl group.

57. The compound of claim 50, having a minimum inhibitory concentration (MIC) less than 10 μg/mL against at least one Gram-positive bacterium.

58. The compound of claim 43, 46, 47, 48 or 49, having a minimum inhibitory concentration (MIC) less than 10 μg/mL against at least one Gram-positive bacterium.

59. A compound represented by the following general formula:



wherein

R_3, R_5, R_6, R_7, R_8, R_{21}, R_{22}, R_1', R_2', R_4', R_5', R_6', and R_7', for each occurrence, independently represent hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine.

acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

R_{80} represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

60. The compound of claim 59, wherein

R_2' and R_3 independently for each occurrence represent H or a hydrophobic aliphatic group;

R_5, R_6, R_7 and R_8 independently for each occurrence represent H, C_1-C_6 alkyl, 1-alkenyl, 1-alkynyl, aryl, -OR, $-OCF_3$, $-OC(R)_2OR$, $-C(R)_2OR$, $-CO_2R$, or a small hydrophobic moiety;

R_1' represents H, alkyl, aryl, *p*-toluenesulfonyl, $-(CH_2)_nN(Phth)$, or $-(CH_2)_nN(R)_2$; wherein n is an integer in the range 1 to 6 inclusive;

R_4', R_5', R_6' and R_7' independently for each occurrence represent H, or a small hydrophobic moiety; and

R_{21} and R_{22} independently for each occurrence represent H, alkyl, aryl, or $-(CH_2)_m-R_{80}$, or R_{21} and R_{22} taken together with N represent a heterocycle comprising from 4 to 8 members inclusive, with the proviso that R_{21} and R_{22} are selected such that $N(R_{21})R_{22}$ comprises a primary or secondary amine.

61. The compound of claim 60, wherein R_2' and R_3 independently for each occurrence represent H, C_1-C_6 alkyl, or aryl.

62. The compound of claim 60, wherein R_2' and R_3 independently for each occurrence represent H or $-CH_3$.

63. The compound of claim 61, wherein R_5, R_6, R_7 and R_8 independently for each occurrence represent H, halogen, trihalogenated methyl or $-CCR_{60}$, and R_{60} represents hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$.

64. The compound of claim 59, 60, 61, 62 or 63, wherein R_4', R_5', R_6' and R_7' independently for each occurrence represent H, halogen, or a halogenated alkyl.

65. The compound of claim 59, 60, 61, 62 or 63, wherein R_{21} and R_{22} independently for each occurrence represent H, $-(CH_2)_nNH(R_1')$, *ortho*-$CH_2C_6H_4CH_2NH(R_1')$,

meta-$CH_2C_6H_4CH_2NH(R_1')$, or *para*-$CH_2C_6H_4CH_2NH(R_1')$, *ortho*-$CH_2C_6H_4O(R_1')$, *meta*-$CH_2C_6H_4O(R_1')$, or *para*-$CH_2C_6H_4O(R_1')$, *ortho*-$CH_2C_6H_4OMe$, *meta*-$CH_2C_6H_4OMe$, or *para*-$CH_2C_6H_4OMe$, *ortho*-, *meta*-, or *para*-$CH_2C_6H_4OH$, (2-benzimidazolyl)CH_2-, 2-methoxyphenyl, 3-methoxyphenyl, or 4-methoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, or 4-hydroxyphenyl, or 2((R_1')aminomethyl)cyclohexylmethyl, 3((R_1')aminomethyl)cyclohexylmethyl, or 4-((R_1')aminomethyl)cyclohexylmethyl; wherein n is an integer in the range 1 to 6 inclusive

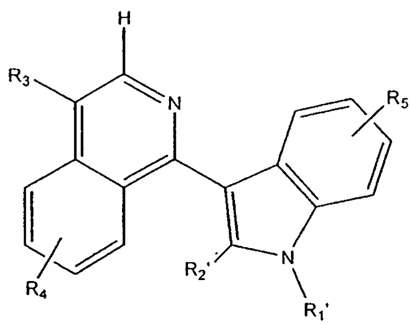
66. The compound of claim 59, 60, 61, 62 or 63, having a minimum inhibitory concentration (MIC) less than 10 μg/mL against at least one Gram-positive bacterium.

67. The compound of claim 52, having a minimum inhibitory concentration (MIC) less than 1 μg/mL against at least one Gram-positive bacterium.

68. The compound of claim 52, having a minimum inhibitory concentration (MIC) less than 0.1 μg/mL against at least one Gram-positive bacterium.

69. The compound of claim 52, having a therapeutic index in primates of at least 10 for the inhibition of infection by at least one Gram-positive bacterium.

70. The compound represented by general formula 3:



3

wherein

R_3, R_1', and R_2', for each occurrence, independently represent hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

R_4, and R_5, for each occurrence, independently represent halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl,

phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

the B-rings of the 1-isoquinolinyl and 3-indolyl moieties may be unsubstituted or substituted between one and four times inclusive by R_4 and R_5, respectively;

R_{80} represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle , or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

71. The compound of claim 70, wherein

R_1' represents H, alkyl, aryl, Me, *p*-toluenesulfonyl, $-(CH_2)_nN(Phth)$, or $-(CH_2)_nN(R)_2$; wherein n is an integer in the range 1 to 6 inclusive;

R_2'and R_3 independently for each occurrence represent H or a hydrophobic aliphatic group;

R_4 independently for each occurrence represents C_1-C_6 alkyl, 1-alkenyl, 1-alkynyl, aryl, -OR, $-OCF_3$, $-OC(R)_2OR$, $-C(R)_2OR$, $-CO_2R$, or a small hydrophobic moiety; and

R_5 independently for each occurrence represents a small hydrophobic moiety, $-C(O)N(R)_2$, -CN, $-NO_2$, -OH, -OR, $-O_2$Caryl, or $-O_2$Calkyl.

72. The compound of claim 71, wherein R_2'and R_3 independently for each occurrence represent H, C_1-C_6 alkyl, or aryl.

73. The compound of claim 72, wherein R_2'and R_3 independently for each occurrence represent H or $-CH_3$.

74. The compound of claim 70, 71 or 72, wherein R_4 independently for each occurrence represents a halogen, trihalogenated methyl or $-CCR_{60}$; and R_{60} represents hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, aminoalkyl, alkylamino, sulfhydryl, alkylthio, imine, amide, carbonyl, carboxyl, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, heteroalkyl, nitrile, amidine, amine oxide, aryl, heteroaryl, carbamate, imide, oxime, sulfonamide, thioamide, urea, or $-(CH_2)_m-R_{80}$.

75. The compound of claim 70, 71 or 72, wherein R_5 independently for each occurrence represents a small hydrophobic moiety, $-C(O)N(R)_2$, -CN, $-NO_2$, -OH, -OR, $-O_2$Caryl, or $-O_2$Calkyl.

76. The compound of claim 75, wherein R_5 independently for each occurrence represents a halogen, a trihalogenated methyl, $-C(O)N(R)_2$, -CN, $-NO_2$, -OH, -OR, $-O_2$Caryl, or $-O_2$Calkyl.

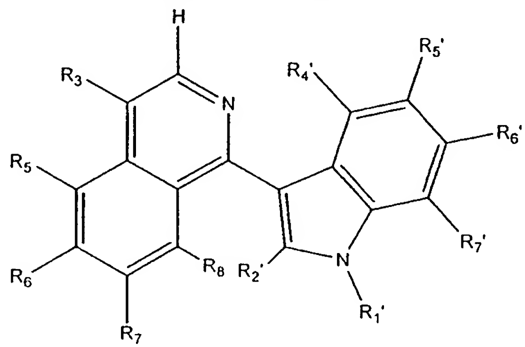
77. The compound of claim 70, 71, 72 or 73, having a minimum inhibitory concentration (MIC) less than 10 μg/mL against at least one Gram-positive bacterium.

78. The compound of claim 77, having a minimum inhibitory concentration (MIC) less than 1 μg/mL against at least one Gram-positive bacterium.

79. The compound of claim 77, having a minimum inhibitory concentration (MIC) less than 0.1 μg/mL against at least one Gram-positive bacterium.

80. The compound of claim 77, having a therapeutic index in primates of at least 10 for the inhibition of infection by at least one Gram-positive bacterium.

81. The compound represented by the following general structure:



wherein

R_2' and R_3 independently for each occurrence represent H, C_1-C_6 alkyl, or aryl;

R_5, R_6, R_7, and R_8 independently for each occurrence represent H, C_1-C_6 alkyl, 1-alkenyl, 1-alkynyl, aryl, -C(O)N(R)$_2$, or a small hydrophobic moiety;

R_1' represents H, alkyl, aryl, Me, or *p*-toluenesulfonyl; and

R_4', R_5', R_6' and R_7' independently for each occurrence represent H, or a small hydrophobic moiety, -C(O)NR$_2$, -CN, -NO$_2$, -OH, -OR, -O$_2$Caryl, or -O$_2$Calkyl.

82. The compound of claim 81, wherein

R_2' and R_3 independently for each occurrence represent H, Me, or aryl;

R_5, R_6, R_7, and R_8 independently for each occurrence represent H, a halogen, trihalogenated methyl, or -CCR$_{60}$ (wherein R_{60} is defined elsewhere);

R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a halogen, a halogenated alkyl, -C(O)NR$_2$, -CN, -NO$_2$, -OH, -OR, -O$_2$Caryl, or -O$_2$Calkyl.

83. The compound of claim 82, wherein R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a halogen, or a trifluoromethyl group.

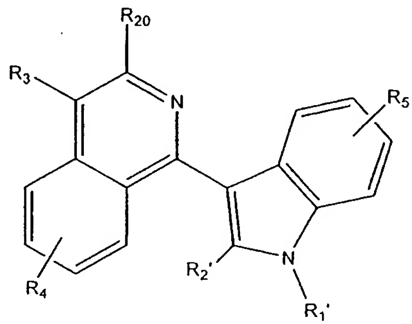
84. The compound of claim 81, 82 or 83, having a minimum inhibitory concentration (MIC) less than 10 μg/mL against at least one Gram-positive bacterium.

85. The compound of claim 84, having a minimum inhibitory concentration (MIC) less than 1 μg/mL against at least one Gram-positive bacterium.

86. The compound of claim 84, having a minimum inhibitory concentration (MIC) less than 0.1 μg/mL against at least one Gram-positive bacterium.

87. The compound of claim 84, having a therapeutic index in primates of at least 10 for the inhibition of infection by at least one Gram-positive bacterium.

88. The compound represented by general formula 4:



4

wherein

R_{20} represents H, Me, lower alkyl, halogen, -C(Z)OR, -C(Z)N(R)$_2$, -S(Z)$_2$N(R)$_2$, or -P(Z)$_2$N(R)$_2$, wherein Z independently for each occurrence represents (R)$_2$, O, S, or NR;

R, R_3, R_1', and R_2', for each occurrence, independently represent hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or -$(CH_2)_m$-R_{80};

R_4, and R_5, for each occurrence, independently represent halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or -$(CH_2)_m$-R_{80};

the B-rings of the 1-isoquinolinyl and 3-indolyl moieties may be unsubstituted or substituted between one and four times inclusive by R_4 and R_5, respectively;

R_{80} represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle , or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

89. The compound of claim 88, wherein R_{20} represents halogen, -C(Z)OR, or -C(Z)N(R)$_2$, and Z independently for each occurrence represents (R)$_2$, O, S, or NR.

90. The compound of claim 88, wherein

R_1' represents H, alkyl, aryl, Me, or *p*-toluenesulfonyl;

R_2' and R_3 independently for each occurrence represent H, Me, C_1-C_6 alkyl, or aryl;

R_4 independently for each occurrence represents Me, C_1-C_6 alkyl, 1-alkenyl, 1-alkynyl, aryl, -OR, -OCF_3, -OCR_2OR, -CR_2OR, -CO_2R, or a small hydrophobic moiety; and

R_5 independently for each occurrence represents a small hydrophobic moiety, -C(O)NR_2, -CN, -NO_2, -OH, -OR, -O_2Caryl, or -O_2Calkyl.

91. The compound of claim 90, wherein

R_1' represents H, alkyl, aryl, or *p*-toluenesulfonyl; and

R_2' and R_3 independently for each occurrence represent H, Me, or aryl.

92. The compound of claim 91, wherein R_1' represents H, or Me.

93. The compound of claim 92, wherein R_2' and R_3 independently for each occurrence represent H, or Me.

94. The compound of claim 88, 89 or 90, wherein R_4 independently for each occurrence represents Me, a halogen, a halogenated alkyl, or -CCR_{60}, R_{60} represents hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, aminoalkyl, alkylamino, sulfhydryl, alkylthio, imine, amide, carbonyl, carboxyl, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, heteroalkyl, nitrile, amidine, amine oxide, aryl, heteroaryl, carbamate, imide, oxime, sulfonamide, thioamide, urea, or -$(CH_2)_m$-R_{80}.

95. The compound of claim 94, wherein R_4 independently for each occurrence represents a halogen, or a trifluoromethyl group.

96. The compound of claim 88, 89 or 90, wherein R_5 independently for each occurrence represents a small hydrophobic moiety, -C(O)NR_2, -CN, -NO_2, -OH, -OR, -O_2Caryl, or -O_2Calkyl.

97. The compound of claim 96, wherein R_5 independently for each occurrence represents a halogen, a halogenated alkyl, -C(O)NR_2, -CN, -NO_2, -OH, -OR, -O_2Caryl, or -O_2Calkyl.

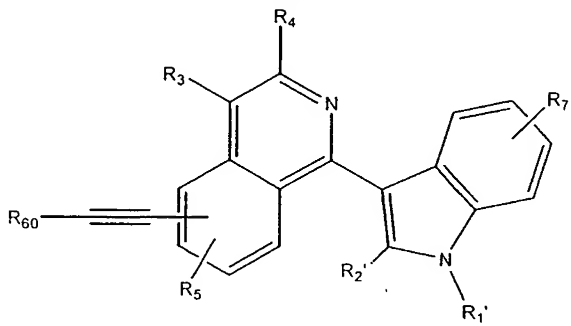
98. The compound of claim 88, 89 or 90, having a minimum inhibitory concentration (MIC) less than 10 μg/mL against at least one Gram-positive bacterium.

99. The compound of claim 98, having a minimum inhibitory concentration (MIC) less than 1 μg/mL against at least one Gram-positive bacterium.

100. The compound of claim 98, having a minimum inhibitory concentration (MIC) less than 0.1 μg/mL against at least one Gram-positive bacterium.

101. The compound of claim 98, having a therapeutic index in primates of at least 10 for the inhibition of infection by at least one Gram-positive bacterium.

102. The compound represented by the following general formula:



wherein

R_3, R_4, R_1', R_2', and R_{60} for each occurrence, independently represent hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

R_5, and R_7, for each occurrence, independently represent halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

the B-ring of the 1-isoquinolinyl moiety may be unsubstituted beyond the alkynyl group or substituted between one and three times inclusive by R_5;

the B-ring of the 3-indolyl moiety may be unsubstituted or substituted between one and four times inclusive by R_7;

R_{80} represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle , or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

103. The compound of claim 102, wherein

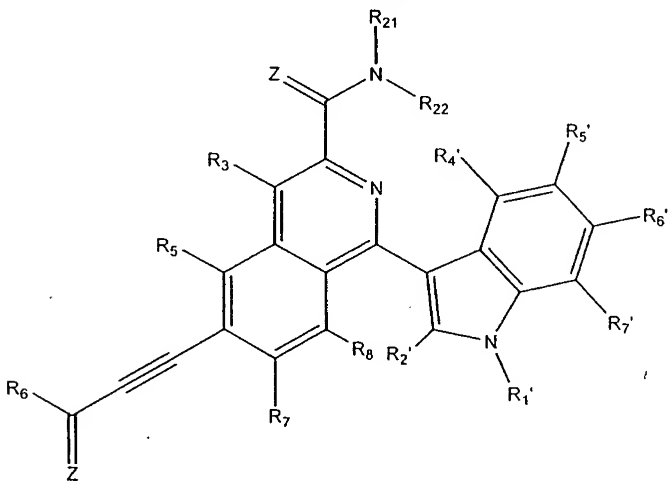
R_1' represents H, alkyl, aryl, Me, or *p*-toluenesulfonyl;

R_2', R_3, and R_4 independently for each occurrence represent H, Me, C_1-C_6 alkyl, or aryl;

R_5 independently for each occurrence represents Me, C_1-C_6 alkyl, 1-alkenyl, 1-alkynyl, aryl, -OR, $-OCF_3$, $-OCR_2OR$, $-CR_2OR$, $-CO_2R$, or a small hydrophobic moiety; and

R_7 independently for each occurrence represents a small hydrophobic moiety, $-C(O)NR_2$, -CN, $-NO_2$, -OH, -OR, $-O_2$Caryl, or $-O_2$Calkyl.

104. The compound represented by the following general structure:



wherein

Z independently for each occurrence represents $(R)_2$, O, S, or NR;

R_5, R_7, and R_8 independently for each occurrence represent H, Me, C_1-C_6 alkyl, heteroalkyl, 1-alkenyl, 1-alkynyl, aryl, heteroaryl, -OR, $-OCF_3$, $-OCR_2OR$, $-CR_2OR$, $-CO_2R$, or a small hydrophobic moiety;

R_6 is selected from the group comprising NHR, $N(R)_2$, 1-piperidyl, 1-piperazinyl, 1-pyrrolidinyl, 2-phenylethylamino, 4-morpholinyl, and 4-phenylmethyl-1-piperidyl;

R_1' represents H, alkyl, aryl, *p*-toluenesulfonyl, $-(CH_2)_nN(Phth)$, or $-(CH_2)_nN(R)_2$; wherein n is an integer in the range 1 to 6 inclusive;

R_2' and R_3 independently for each occurrence represent H, Me, C_1-C_6 alkyl, or aryl;

R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a small hydrophobic moiety, -C(O)NR_2, -CN, -NO_2, -OH, -OR, -O_2Caryl, or -O_2Calkyl; and

R_{21} and R_{22} independently for each occurrence represent H, alkyl, heteroalkyl, aryl, heteroaryl, -$(CH_2)_m$-R_{80}, and more preferably -$(CH_2)_n N(R_1')_2$, wherein n is an integer in the range 1 to 6 inclusive, *ortho-*, *meta-*, or *para-*$CH_2C_6H_4CH_2N(R_1')_2$, *ortho-*, *meta-*, or *para-*$C_6H_4CH_2N(R_1')_2$, *ortho-*, *meta-*, or *para-*$CH_2C_6H_4O(R_1')$, *ortho-*, *meta-*, or *para-*$CH_2C_6H_4OMe$, *ortho-*, *meta-*, or *para-*$CH_2C_6H_4OH$, (2-benzimidazolyl)CH_2-, 2-, 3-, or 4-(R_1')Ophenyl, 2-, 3-, or 4-methoxyphenyl, 2-, 3-, or 4-hydroxyphenyl, or 2-, 3-, or 4-((R_1')$_2$NCH_2)cyclohexylmethyl, or 2-, 3-, or 4-((R_1')$_2$N)cyclohexylmethyl; or N(R_{21})R_{22} taken together represent a heterocycle comprising from 4 to 8 members inclusive.

105. The compound of claim 104, wherein R_2' and R_3 independently for each occurrence represent H, C_1-C_6 alkyl, or aryl.

106. The compound of claim 105, wherein R_2' and R_3 independently for each occurrence represent H, -CH_3, or phenyl.

107. The compound of claim 104, 105 or 106, wherein R_5, R_7 and R_8 independently for each occurrence represent H, halogen, trihalogenated methyl or -CCR_{60} and R_{60} represents hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, aminoalkyl, alkylamino, sulfhydryl, alkylthio, imine, amide, carbonyl, carboxyl, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, heteroalkyl, nitrile, amidine, amine oxide, aryl, heteroaryl, carbamate, imide, oxime, sulfonamide, thioamide, urea, or -$(CH_2)_m$-R_{80}..

108. The compound of claim 104, 105 or 106, wherein R_4', R_5', R_6' and R_7' independently for each occurrence represent H, halogen, or a halogenated alkyl.

109. The compound of claim 108, wherein R_4', R_5', R_6' and R_7' independently for each occurrence represent H, halogen, or trifluoromethyl.

110. The compound of claim 104, 105 or 106, wherein R_{21} and R_{22} independently for each occurrence represent H, -$(CH_2)_n NH(R_1')$, *ortho*-$CH_2C_6H_4CH_2NH(R_1')$, *meta*-$CH_2C_6H_4CH_2NH(R_1')$, or *para*-$CH_2C_6H_4CH_2NH(R_1')$, *ortho*-$CH_2C_6H_4O(R_1')$, *meta*-$CH_2C_6H_4O(R_1')$, or *para*-$CH_2C_6H_4O(R_1')$, *ortho*-$CH_2C_6H_4OMe$, *meta*-$CH_2C_6H_4OMe$, or *para*-$CH_2C_6H_4OMe$, *ortho-*, *meta-*, or *para*-$CH_2C_6H_4OH$, (2-benzimidazolyl)CH_2-, 2-methoxyphenyl, 3-methoxyphenyl, or 4-methoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, or 4-hydroxyphenyl, or 2((R_1')aminomethyl)cyclohexylmethyl, 3((R_1')aminomethyl)cyclohexylmethyl, or 4-((R_1')aminomethyl)cyclohexylmethyl; wherein n is an integer in the range 1 to 6 inclusive

111 The compound of claim 104, 105 or 106, wherein R_6 is selected from the group comprising NHR, N(R)$_2$, 1-piperidyl, 1-piperazinyl, 1-pyrrolidinyl, 2-phenylethylamino, 4-morpholinyl, and 4-phenylmethyl-1-piperidyl.

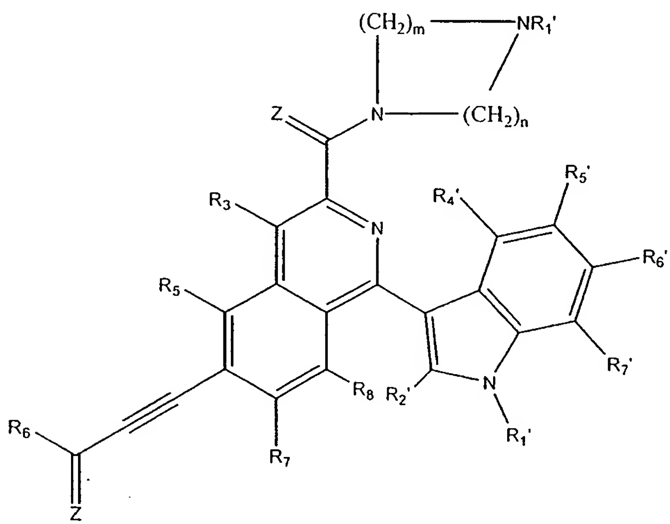
112.. The compound of claim 104, 105 or 106, having a minimum inhibitory concentration (MIC) less than 10 μg/mL against at least one Gram-positive bacterium.

113. The compound of claim 112, having a minimum inhibitory concentration (MIC) less than 1 μg/mL against at least one Gram-positive bacterium.

114. The compound of claim 112, having a minimum inhibitory concentration (MIC) less than 0.1 μg/mL against at least one Gram-positive bacterium.

115. The compound of claim 112, having a therapeutic index in primates of at least 10 for the inhibition of infection by at least one Gram-positive bacterium.

116. The compound represented by the following general structure:



wherein

Z independently for each occurrence represents $(R)_2$, O, S, or NR;

R_5, R_7, and R_8 independently for each occurrence represent H, Me, C_1-C_6 alkyl, heteroalkyl, 1-alkenyl, 1-alkynyl, aryl, heteroaryl, -OR, $-OCF_3$, $-OCR_2OR$, $-CR_2OR$, $-CO_2R$, or a small hydrophobic moiety;

R_6 is selected from the group comprising NHR, $N(R)_2$, 1-piperidyl, 1-piperazinyl, 1-pyrrolidinyl, 2-phenylethylamino, 4-morpholinyl, and 4-phenylmethyl-1-piperidyl;

R_1' represents H, alkyl, aryl, *p*-toluenesulfonyl, $-(CH_2)_nN(Phth)$, or $-(CH_2)_nN(R)_2$; wherein n is an integer in the range 1 to 6 inclusive;

R_2' and R_3 independently for each occurrence represent H, Me, C_1-C_6 alkyl, or aryl;

R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a small hydrophobic moiety, -C(O)NR_2, -CN, -NO_2, -OH, -OR, -O_2Caryl, or -O_2Calkyl; and

m and n are integers independently selected from the range 1 to 4 inclusive.

117. The compound of claim 116, wherein R_2' and R_3 independently for each occurrence represent H, Me, or phenyl.

118. The compound of claim 116 and 117, wherein R_5, R_7, and R_8 independently for each occurrence represent H, Me, -OR, -OCF_3, -OCR_2OR, -CR_2OR, -CO_2R,. a halogen, or a halogenated alkyl.

119. The compound of claim 116 or 117, wherein R_5, R_7, and R_8 independently for each occurrence represent H, Me, a halogen, or trifluoromethyl.

120. The compound of claim 116 or 117, wherein R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a halogen, a halogenated alkyl, -C(O)NR_2, -CN, -NO_2, -OH, -OR, -O_2Caryl, or -O_2Calkyl.

121. The compound of claim 116 or 117, wherein R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a halogen, a trifluoromethyl, -C(O)NR_2, -CN, -NO_2, -OH, -OR, -O_2Caryl, or -O_2Calkyl.

122. The compound of claim 116 or 117, wherein R_6 is selected from the group comprising NHR, $N(R)_2$, 1-piperidyl, 1-piperazinyl, 1-pyrrolidinyl, 2-phenylethylamino, 4-morpholinyl, and 4-phenylmethyl-1-piperidyl.

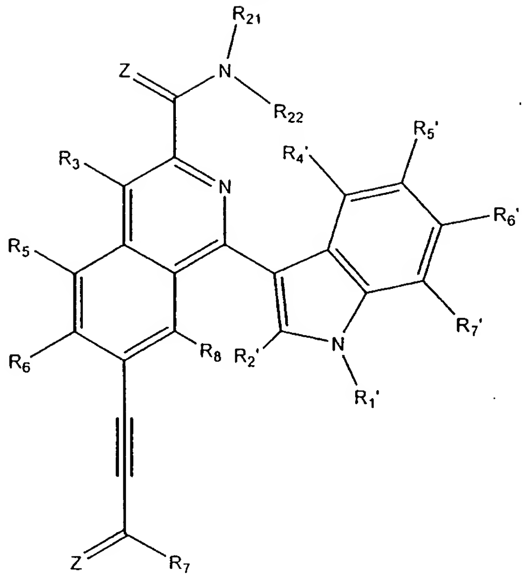
123. The compound of claim 116 or 116, having a minimum inhibitory concentration (MIC) less than 10 µg/mL against at least one Gram-positive bacterium.

124. The compound of claim 123, having a minimum inhibitory concentration (MIC) less than 1 µg/mL against at least one Gram-positive bacterium.

125. The compound of claim 123, having a minimum inhibitory concentration (MIC) less than 0.1 µg/mL against at least one Gram-positive bacterium.

126. The compound of claim 123, having a therapeutic index in primates of at least 10 for the inhibition of infection by at least one Gram-positive bacterium.

127. The compound represented by the following general structure:



wherein

Z independently for each occurrence represents $(R)_2$, O, S, or NR;

R_5, R_6, and R_8 independently for each occurrence represent H, Me, C_1-C_6 alkyl, heteroalkyl, 1-alkenyl, 1-alkynyl, aryl, heteroaryl, -OR, $-OCF_3$, $-OCR_2OR$, $-CR_2OR$, $-CO_2R$, or a small hydrophobic moiety;

R_7 is selected from the group comprising NHR, $N(R)_2$, 1-piperidyl, 1-piperazinyl, 1-pyrrolidinyl, 2-phenylethylamino, 4-morpholinyl, and 4-phenylmethyl-1-piperidyl;

R_1' represents H, alkyl, aryl, *p*-toluenesulfonyl, $-(CH_2)_nN(Phth)$, or $-(CH_2)_nN(R)_2$ wherein n is an integer in the range 1 to 6 inclusive;

R_2' and R_3 independently for each occurrence represent H, Me, C_1-C_6 alkyl, or aryl;

R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a small hydrophobic moiety, $-C(O)NR_2$, -CN, $-NO_2$, -OH, -OR, $-O_2$Caryl, or $-O_2$Calkyl; and

R_{21} and R_{22} independently for each occurrence represent H, alkyl, heteroalkyl, aryl, heteroaryl, $-(CH_2)_m-R_{80}$, and more preferably $-(CH_2)_nN(R_1')_2$, wherein n is an integer in the range 1 to 6 inclusive, *ortho*-, *meta*-, or *para*-$CH_2C_6H_4CH_2N(R_1')_2$, *ortho*-, *meta*-, or *para*-$C_6H_4CH_2N(R_1')_2$, *ortho*-, *meta*-, or *para*-$CH_2C_6H_4O(R_1')$, *ortho*-, *meta*-, or *para*-$CH_2C_6H_4OMe$, *ortho*-, *meta*-, or *para*-$CH_2C_6H_4OH$, (2-benzimidazolyl)CH_2-, 2-, 3-, or 4-(R_1')Ophenyl, 2-, 3-, or 4-methoxyphenyl, 2-, 3-, or 4-hydroxyphenyl, or 2-, 3-, or 4-$((R_1')_2NCH_2)$cyclohexylmethyl, or 2-, 3-, or 4-$((R_1')_2N)$cyclohexylmethyl; or $N(R_{21})R_{22}$ taken together represent a heterocycle comprising from 4 to 8 members inclusive.

128. The compound of claim 127, wherein R_2' and R_3 independently for each occurrence represent H, Me, or phenyl.

129. The compound of claim 127, wherein R_5, R_6, and R_8 independently for each occurrence represent H, Me, -OR, $-OCF_3$, $-OCR_2OR$, $-CR_2OR$, $-CO_2R$, a halogen, or a halogenated alkyl.

130. The compound of claim 129, wherein R_5, R_6, and R_8 independently for each occurrence represent H, Me, a halogen, or trifluoromethyl.

131. The compound of claim 127, wherein R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a halogen, a halogenated alkyl, $-C(O)NR_2$, -CN, $-NO_2$, -OH, -OR, $-O_2$Caryl, or $-O_2$Calkyl.

132. The compound of claim 131, wherein R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a halogen, or a trifluoromethyl.

133. The compound of claim 127, wherein R_7 is selected from the group comprising NHR, $N(R)_2$, 1-piperidyl, 1-piperazinyl, 1-pyrrolidinyl, 2-phenylethylamino, 4-morpholinyl, and 4-phenylmethyl-1-piperidyl.

134. The compound of claim 127, wherein R_{21} and R_{22} independently for each occurrence represent H, $-(CH_2)_nNH(R_1')$, *ortho*-$CH_2C_6H_4CH_2NH(R_1')$, *meta*-$CH_2C_6H_4CH_2NH(R_1')$, or *para*-$CH_2C_6H_4CH_2NH(R_1')$, *ortho*-$CH_2C_6H_4O(R_1')$, *meta*-$CH_2C_6H_4O(R_1')$, or *para*-$CH_2C_6H_4O(R_1')$, *ortho*-$CH_2C_6H_4OMe$, *meta*-$CH_2C_6H_4OMe$, or *para*-$CH_2C_6H_4OMe$, *ortho*-, *meta*-, or *para*-$CH_2C_6H_4OH$, (2-benzimidazolyl)CH_2-, 2-methoxyphenyl, 3-methoxyphenyl, or 4-methoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, or 4-hydroxyphenyl, or 2((R_1')aminomethyl)cyclohexylmethyl, 3((R_1')aminomethyl)cyclohexylmethyl, or 4-((R_1')aminomethyl)cyclohexylmethyl; wherein n is an integer in the range 1 to 6 inclusive

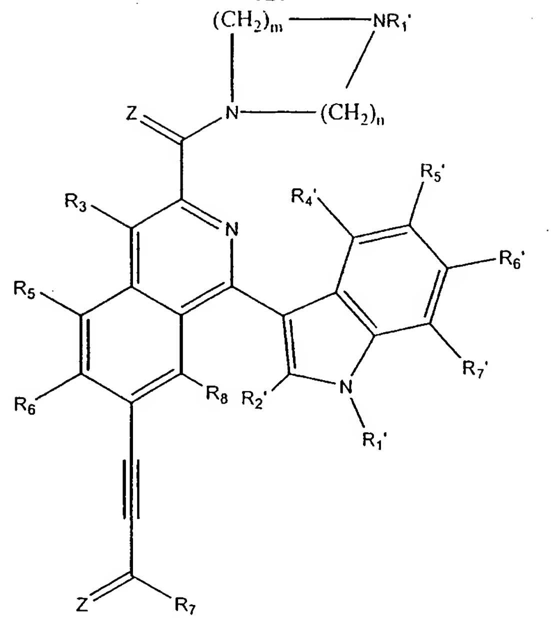
135. The compound of claim 127, having a minimum inhibitory concentration (MIC) less than 10 μg/mL against at least one Gram-positive bacterium.

136. The compound of claim 127, having a minimum inhibitory concentration (MIC) less than 1 μg/mL against at least one Gram-positive bacterium.

137. The compound of claim 127, having a minimum inhibitory concentration (MIC) less than 0.1 μg/mL against at least one Gram-positive bacterium.

138. The compound of claim 127, having a therapeutic index in primates of at least 10 for the inhibition of infection by at least one Gram-positive bacterium.

139. The compound represented by the following general formula:



wherein

Z independently for each occurrence represents $(R)_2$, O, S, or NR;

R_5, R_6, and R_8 independently for each occurrence represent H, Me, C_1-C_6 alkyl, heteroalkyl, 1-alkenyl, 1-alkynyl, aryl, heteroaryl, -OR, $-OCF_3$, $-OCR_2OR$, $-CR_2OR$, $-CO_2R$, or a small hydrophobic moiety;

R_7 is selected from the group comprising NHR, $N(R)_2$, 1-piperidyl, 1-piperazinyl, 1-pyrrolidinyl, 2-phenylethylamino, 4-morpholinyl, and 4-phenylmethyl-1-piperidyl;

R_1' represents H, alkyl, aryl, *p*-toluenesulfonyl, $-(CH_2)_nN(Phth)$, or $-(CH_2)_nN(R)_2$; wherein n is an integer in the range 1 to 6 inclusive;

R_2' and R_3 independently for each occurrence represent H, Me, C_1-C_6 alkyl, or aryl;

R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a small hydrophobic moiety, $-C(O)NR_2$, -CN, $-NO_2$, -OH, -OR, $-O_2$Caryl, or $-O_2$Calkyl; and

m and n are integers independently selected from the range 1 to 4 inclusive.

140. The compound of claim 139, wherein R_2' and R_3 independently for each occurrence represent H, Me, or phenyl.

141. The compound of claim 139 or 140, wherein R_5, R_6, and R_8 independently for each occurrence represent H, Me, -OR, $-OCF_3$, $-OCR_2OR$, $-CR_2OR$, $-CO_2R$, a halogen, or a halogenated alkyl.

142. The compound of claim 141, wherein R_5, R_6, and R_8 independently for each occurrence represent H, Me, a halogen, or trifluoromethyl.

143. The compound of claim 139 or 140, wherein R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a halogen, a halogenated alkyl, $-C(O)NR_2$, -CN, $-NO_2$, -OH, -OR, $-O_2Caryl$, or $-O_2Calkyl$.

144. The compound of claim 143, wherein R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a halogen, a trifluoromethyl, $-C(O)NR_2$, -CN, $-NO_2$, -OH, -OR, $-O_2Caryl$, or $-O_2Calkyl$.

145. The compound of claim 139, wherein R_7 is selected from the group comprising NHR, $N(R)_2$, 1-piperidyl, 1-piperazinyl, 1-pyrrolidinyl, 2-phenylethylamino, 4-morpholinyl, and 4-phenylmethyl-1-piperidyl.

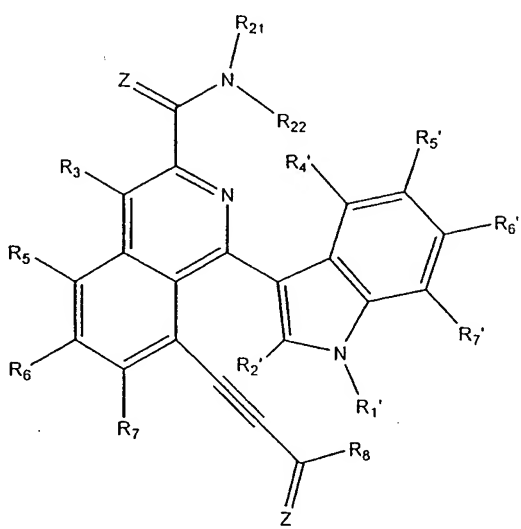
146. The compound of claim 139, having a minimum inhibitory concentration (MIC) less than 10 μg/mL against at least one Gram-positive bacterium.

147. The compound of claim 139, having a minimum inhibitory concentration (MIC) less than 1 μg/mL against at least one Gram-positive bacterium.

148. The compound of claim 139, having a minimum inhibitory concentration (MIC) less than 0.1 μg/mL against at least one Gram-positive bacterium.

149. The compound of claim 139, having a therapeutic index in primates of at least 10 for the inhibition of infection by at least one Gram-positive bacterium.

150. The compound represented by the following general structure:



wherein

Z independently for each occurrence represents $(R)_2$, O, S, or NR;

R_5, R_6, and R_7 independently for each occurrence represent H, Me, C_1-C_6 alkyl, heteroalkyl, 1-alkenyl, 1-alkynyl, aryl, heteroaryl, -OR, $-OCF_3$, $-OCR_2OR$, $-CR_2OR$, $-CO_2R$, or a small hydrophobic moiety;

R_8 is selected from the group comprising NHR, $N(R)_2$, 1-piperidyl, 1-piperazinyl, 1-pyrrolidinyl, 2-phenylethylamino, 4-morpholinyl, and 4-phenylmethyl-1-piperidyl ;

R_1' represents H, alkyl, aryl, *p*-toluenesulfonyl, $-(CH_2)_nN(Phth)$, or $-(CH_2)_nN(R)_2$; wherein n is an integer in the range 1 to 6 inclusive;

R_2' and R_3 independently for each occurrence represent H, Me, C_1-C_6 alkyl, or aryl;

R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a small hydrophobic moiety, $-C(O)NR_2$, -CN, $-NO_2$, -OH, -OR, $-O_2C$aryl, or $-O_2C$alkyl; and

R_{21} and R_{22} independently for each occurrence represent H, alkyl, heteroalkyl, aryl, heteroaryl, $-(CH_2)_m-R_{80}$, and more preferably $-(CH_2)_nN(R_1')_2$, wherein n is an integer in the range 1 to 6 inclusive, *ortho-*, *meta-*, or *para*-$CH_2C_6H_4CH_2N(R_1')_2$, *ortho-*, *meta-*, or *para*-$C_6H_4CH_2N(R_1')_2$, *ortho-*, *meta-*, or *para*-$CH_2C_6H_4O(R_1')$, *ortho-*, *meta-*, or *para*-$CH_2C_6H_4OMe$, *ortho-*, *meta-*, or *para*-$CH_2C_6H_4OH$, (2-benzimidazolyl)CH_2-, 2-, 3-, or 4-(R_1')Ophenyl, 2-, 3-, or 4-methoxyphenyl, 2-, 3-, or 4-hydroxyphenyl, or 2-, 3-, or 4-((R_1')$_2$NCH$_2$)cyclohexylmethyl, or 2-, 3-, or 4-((R_1')$_2$N)cyclohexylmethyl; or $N(R_{21})R_{22}$ taken together represent a heterocycle comprising from 4 to 8 members inclusive.

151. The compound of claim 150, wherein R_2' and R_3 independently for each occurrence represent H, Me, or phenyl.

152. The compound of claim 150, wherein R_5, R_6, and R_7 independently for each occurrence represent H, Me, -OR, $-OCF_3$, $-OCR_2OR$, $-CR_2OR$, $-CO_2R$, a halogen, or a halogenated alkyl.

153. The compound of claim 152, wherein R_5, R_6, and R_7 independently for each occurrence represent H, Me, a halogen, or trifluoromethyl.

154. The compound of claim 150, wherein R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a halogen, a halogenated alkyl, $-C(O)NR_2$, -CN, $-NO_2$, -OH, -OR, $-O_2C$aryl, or $-O_2C$alkyl.

155. The compound of claim 154, wherein R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a halogen, or a trifluoromethyl.

156. The compound of claim 150, wherein R_8 is selected from the group comprising NHR, $N(R)_2$, 1-piperidyl, 1-piperazinyl, 1-pyrrolidinyl; 2-phenylethylamino, 4-morpholinyl, and 4-phenylmethyl-1-piperidyl.

157. The compound of claim 150, wherein wherein R_{21} and R_{22} independently for each occurrence represent H, $-(CH_2)_nNH(R_1')$, *ortho*-$CH_2C_6H_4CH_2NH(R_1')$, *meta*-$CH_2C_6H_4CH_2NH(R_1')$, or *para*-$CH_2C_6H_4CH_2NH(R_1')$, *ortho*-$CH_2C_6H_4O(R_1')$, *meta*-$CH_2C_6H_4O(R_1')$, or *para*-$CH_2C_6H_4O(R_1')$, *ortho*-$CH_2C_6H_4OMe$, *meta*-$CH_2C_6H_4OMe$, or *para*-$CH_2C_6H_4OMe$, *ortho*-, *meta*-, or *para*-$CH_2C_6H_4OH$, (2-benzimidazolyl)CH_2-, 2-methoxyphenyl, 3-methoxyphenyl, or 4-methoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, or 4-hydroxyphenyl, or 2((R_1')aminomethyl)cyclohexylmethyl, 3((R_1')aminomethyl)cyclohexylmethyl, or 4-((R_1')aminomethyl)cyclohexylmethyl, wherein n is an integer in the range 1 to 6 inclusive

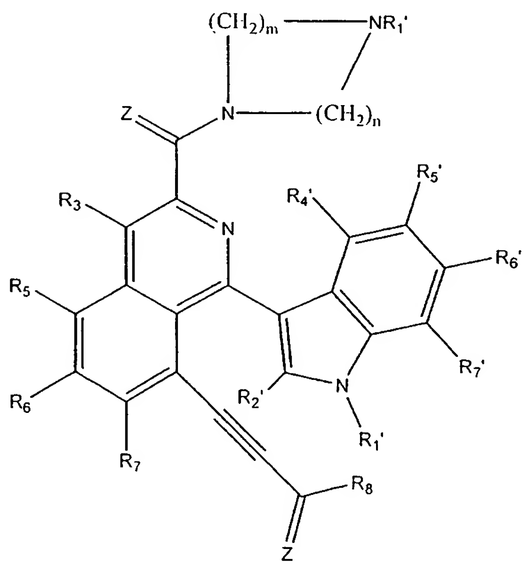
158. The compound of claim 150, having a minimum inhibitory concentration (MIC) less than 10 μg/mL against at least one Gram-positive bacterium.

159. The compound of claim 150, having a minimum inhibitory concentration (MIC) less than 1 μg/mL against at least one Gram-positive bacterium.

160. The compound of claim 150, having a minimum inhibitory concentration (MIC) less than 0.1 μg/mL against at least one Gram-positive bacterium.

161. The compound of claim 150, having a therapeutic index in primates of at least 10 for the inhibition of infection by at least one Gram-positive bacterium.

162. The compound represented by the following general formula:



wherein

Z independently for each occurrence represents $(R)_2$, O, S, or NR;

R_5, R_6, and R_7 independently for each occurrence represent H, Me, C_1-C_6 alkyl, heteroalkyl, 1-alkenyl, 1-alkynyl, aryl, heteroaryl, -OR, $-OCF_3$, $-OCR_2OR$, $-CR_2OR$, $-CO_2R$, or a small hydrophobic moiety;

R_8 is selected from the group comprising NHR, $N(R)_2$, 1-piperidyl, 1-piperazinyl, 1-pyrrolidinyl, 2-phenylethylamino, 4-morpholinyl, and 4-phenylmethyl-1-piperidyl;

R_1' represents H, alkyl, aryl, *p*-toluenesulfonyl, $-(CH_2)_nN(Phth)$, or $-(CH_2)_nN(R)_2$; wherein n is an integer in the range 1 to 6 inclusive;

R_2' and R_3 independently for each occurrence represent H, Me, C_1-C_6 alkyl, or aryl;

R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a small hydrophobic moiety, $-C(O)NR_2$, -CN, $-NO_2$, -OH, -OR, $-O_2$Caryl, or $-O_2$Calkyl; and

m and n are integers independently selected from the range 1 to 4 inclusive.

163. The compound of claim 162, wherein R_2' and R_3 independently for each occurrence represent H, Me, or phenyl.

164. The compound of claim 162, wherein R_5, R_6, and R_7 independently for each occurrence represent H, Me, -OR, $-OCF_3$, $-OCR_2OR$, $-CR_2OR$, $-CO_2R$, a halogen, or a halogenated alkyl.

165. The compound of claim 164, wherein R_5, R_6, and R_7 independently for each occurrence represent H, Me, a halogen, or trifluoromethyl.

166. The compound of claim 162, wherein R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a halogen, a halogenated alkyl, $-C(O)NR_2$, -CN, $-NO_2$, -OH, -OR, $-O_2$Caryl, or $-O_2$Calkyl.

167. The compound of claim 166, wherein R_4', R_5', R_6' and R_7' independently for each occurrence represent H, a halogen, a trifluoromethyl, $-C(O)NR_2$, -CN, $-NO_2$, -OH, -OR, $-O_2$Caryl, or $-O_2$Calkyl.

168. The compound of claim 162, wherein R_8 is selected from the group comprising NHR, $N(R)_2$, 1-piperidyl, 1-piperazinyl, 1-pyrrolidinyl, 2-phenylethylamino, 4-morpholinyl, and 4-phenylmethyl-1-piperidyl.

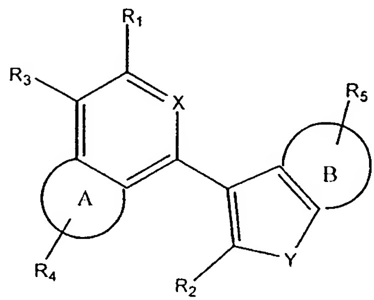
169. The compound of claim 162, having a minimum inhibitory concentration (MIC) less than 10 μg/mL against at least one Gram-positive bacterium.

170. The compound of claim 162, having a minimum inhibitory concentration (MIC) less than 1 μg/mL against at least one Gram-positive bacterium.

171. The compound of claim 162, having a minimum inhibitory concentration (MIC) less than 0.1 μg/mL against at least one Gram-positive bacterium.

172. The compound of claim 162, having a therapeutic index in primates of at least 10 for the inhibition of infection by at least one Gram-positive bacterium.

173. A pharmaceutical preparation comprising, as an active ingredient for inhibition of bacterial cell growth, a compound represented in the general formula 1:



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wherein

each of A and B independently represent fused rings selected from a group consisting of monocyclic or polycyclic cycloalkyls, cycloalkenyls, aryls, and heterocyclic rings, said rings comprising from 4 to 8 atoms in a ring structure;

X represents CR, N, N(O), P, or As;

Y represents CR_2, NR, O, PR, S, AsR, or Se;

R, R_1, R_2, and R_3, for each occurrence, independently represent hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

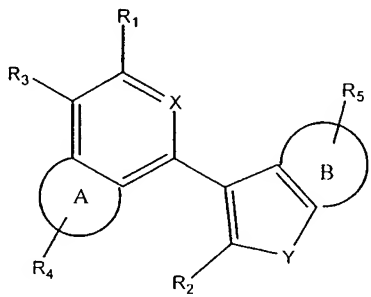
R_4 and R_5, for each occurrence, independently represent halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

A and B independently may be unsubstituted or substituted with R_4 and R_5, respectively, any number of times up to the limitations imposed by stability and the rules of valence;

R_{80} represents an unsubstituted or substituted aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

174. A preparation for topical application to a cutaneous or mucosal tissue, comprising, as an active ingredient for inhibition of bacterial cell growth on the tissue, a compound represented in the general formula **1**:



1

wherein

each of A and B independently represent fused rings selected from a group consisting of monocyclic or polycyclic cycloalkyls, cycloalkenyls, aryls, and heterocyclic rings, said rings comprising from 4 to 8 atoms in a ring structure;

X represents CR, N, N(O), P, or As;

Y represents CR_2, NR, O, PR, S, AsR, or Se;

R, R_1, R_2, and R_3, for each occurrence, independently represent hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

R_4 and R_5, for each occurrence, independently represent halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl,

phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

A and B independently may be unsubstituted or substituted with R_4 and R_5, respectively, any number of times up to the limitations imposed by stability and the rules of valence;

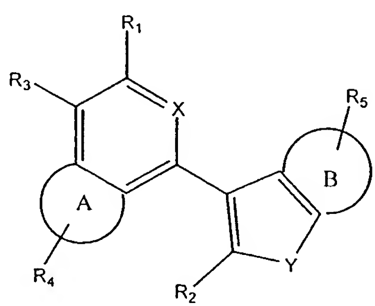
R_{80} represents an unsubstituted or substituted aryl, a cycloalkyl, a cycloalkenyl, a heterocycle , or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

175. The preparation of claim 174, wherein the compound is formulated as a cream, lotion, ointment, liposome dispersion, emulsion, spray, pessary, foam or solution for external application to a cutaneous or mucosal surface.

176. The preparation of claim 174 or 175, wherein the compound is formulated for external application to corneal or dermal surfaces.

177. A method for inhibiting bacterial cell growth comprising contacting bacteria with a compound represented in the general formula 1:



1

wherein

each of A and B independently represent fused rings selected from a group consisting of monocyclic or polycyclic cycloalkyls, cycloalkenyls, aryls, and heterocyclic rings, said rings comprising from 4 to 8 atoms in a ring structure;

X represents CR, N, N(O), P, or As;

Y represents CR_2, NR, O, PR, S, AsR, or Se;

R, R_1, R_2, and R_3, for each occurrence, independently represent hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

R_4 and R_5, for each occurrence, independently represent halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

A and B independently may be unsubstituted or substituted with R_4 and R_5, respectively, any number of times up to the limitations imposed by stability and the rules of valence;

R_{80} represents an unsubstituted or substituted aryl, a cycloalkyl, a cycloalkenyl, a heterocycle , or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

178. The method of claim 177, wherein the bacteria is a Gram-positive bacteria.

179. The method of claim 178, wherein bacteria is selected from the group consisting of Staphylococcus, Streptococcus, Micrococcus, Peptococcus, Peptostreptococcus, Enterococcus, Bacillus, Clostridium, Lactobacillus, Listeria, Erysipelothrix, Propionibacterium, Eubacterium, and Corynebacterium.

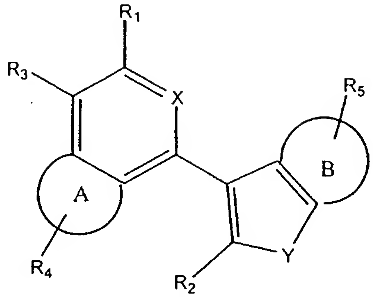
180. The method of claim 177, wherein the bacteria is resistant to methicillin and/or vancomycin.

181. The method of claim 177 or 180, wherein the bacteria is selected from the group consisting of *Staphylococcus spp* and *Enterococcus spp* .

182. The method of claim 177, wherein the bacteria is contacted with the compound *in vitro*.

183. The method of claim 177, wherein the bacteria is contacted with the compound *in vivo*.

184. A method for treating or preventing bacterial infection in an animal, or an external tissue surface thereof, comprising administering a pharmaceutical preparation of a compound represented in the general formula **1**:



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wherein

each of A and B independently represent fused rings selected from a group consisting of monocyclic or polycyclic cycloalkyls, cycloalkenyls, aryls, and heterocyclic rings, said rings comprising from 4 to 8 atoms in a ring structure;

X represents CR, N, N(O), P, or As;

Y represents CR_2, NR, O, PR, S, AsR, or Se;

R, R_1, R_2, and R_3, for each occurrence, independently represent hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

R_4 and R_5, for each occurrence, independently represent halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

A and B independently may be unsubstituted or substituted with R_4 and R_5, respectively, any number of times up to the limitations imposed by stability and the rules of valence;

R_{80} represents an unsubstituted or substituted aryl, a cycloalkyl, a cycloalkenyl, a heterocycle , or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

185. The method of claim 184, wherein the compound is administered to an animal suffering from, or at risk of deveolping, bacteremia, a skin/wound infection, a lower respiratory infection, endocarditis, or infection of the urinary tract.

186. The method of claim 185, wherein the compound is administered parenterally.

187. The method of claim 186, wherein the compound is administered intramuscularly, intravenously, subcutaneously, orally, topically or intranasally.

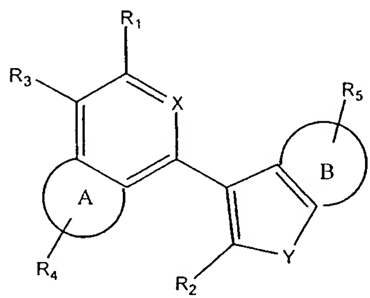
188. The method of claim 185, wherein the compound is administered systemically.

189. The method of claim 184, wherein the compound is administered to a mammal.

190. The method of claim 189, wherein the compound is administered to a primate.

191. The method of claim 189, wherein the compound is administered to a human.

192. A method for promoting weight gain in a livestock, comprising administering to the livestock a compound represented in the general formula **1**:



1

wherein

each of A and B independently represent fused rings selected from a group consisting of monocyclic or polycyclic cycloalkyls, cycloalkenyls, aryls, and heterocyclic rings, said rings comprising from 4 to 8 atoms in a ring structure;

X represents CR, N, N(O), P, or As;

Y represents CR_2, NR, O, PR, S, AsR, or Se;

R, R_1, R_2, and R_3, for each occurrence, independently represent hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate,

epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

R_4 and R_5, for each occurrence, independently represent halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, thiourea, or $-(CH_2)_m-R_{80}$;

A and B independently may be unsubstituted or substituted with R_4 and R_5, respectively, any number of times up to the limitations imposed by stability and the rules of valence;

R_{80} represents an unsubstituted or substituted aryl, a cycloalkyl, a cycloalkenyl, a heterocycle , or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

193. The method of claim 192, wherein the compound is administered systemically.

194. The method of claim 192, wherein the compound is formulated in feedstuff fed to the livestock.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/12706

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D401/04 A61K31/395 C07D401/14 C07D491/04 C07D409/04 C07D471/04 C07D471/08 C07D215/52 C07D209/14 C07D209/12 C07D405/04 C07D40/04 //(C07D491/04,307:00,221:00),

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 574 618 A (AGFA-GEVAERT N.V.) 22 December 1993 see examples 1-3,5; tables 1,2	1
A	US 3 905 982 A (PETER K. YONAN) 16 September 1975 see column 1-2	1,173

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdate of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of theinternational search	Date of mailing of the international search report
12 October 1998	26/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Bijlen, H

1

INTERNATIONAL SEARCH REPORT

Inte. .onal Application No
PCT/US 98/12706

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 (C07D491/04,317:00,221:00),(C07D491/04,319:00,221:00),
(C07D471/08,221:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 October 1998	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Bijlen, H

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 184-194
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 184-194 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/12706

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
EP 574618	A	22-12-1993	DE	69214633	D	21-11-1996
			DE	69214633	T	22-05-1997
US 3905982	A	16-09-1975	AR	202416	A	06-06-1975
			AR	205380	A	30-04-1976
			AT	329563	B	25-05-1976
			AT	602874	A	15-08-1975
			AU	7147074	A	22-01-1976
			BE	817917	A	22-01-1975
			CA	1041501	A	31-10-1978
			CH	605773	A	13-10-1978
			CH	605774	A	13-10-1978
			DE	2435168	A	06-02-1975
			DK	395174	A,B,	10-03-1975
			FR	2238488	A	21-02-1975
			GB	1452398	A	13-10-1976
			IE	39630	B	22-11-1978
			JP	50041873	A	16-04-1975
			NL	7409881	A	27-01-1975
			SE	387341	B	06-09-1976
			SE	7409496	A	24-01-1975
			US	4001244	A	04-01-1977
			US	B571638	I	09-03-1976
			ZA	7404665	A	24-09-1975